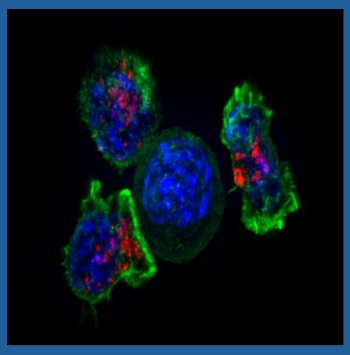
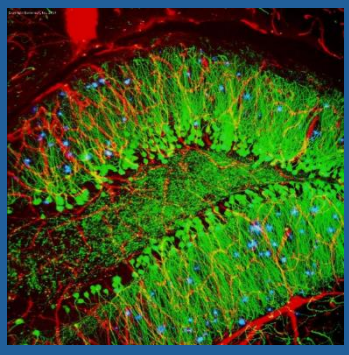
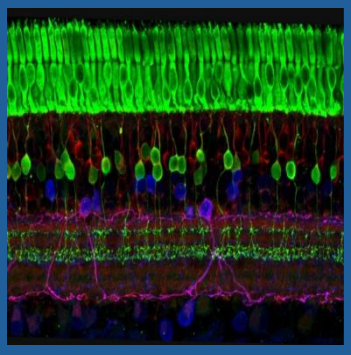
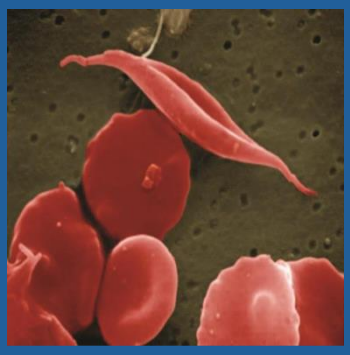
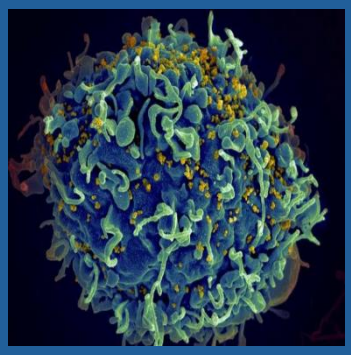
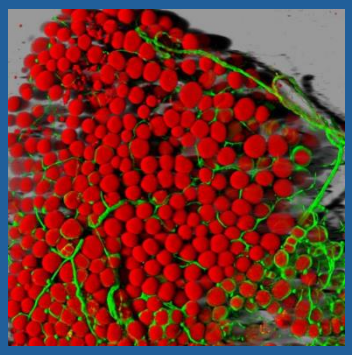
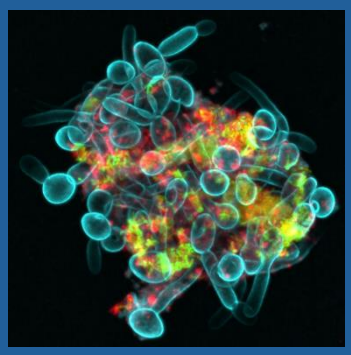
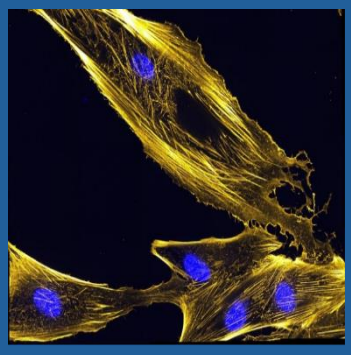
Report of the Director
National Institutes of Health
Fiscal Years 2022 – 2024



National Institutes of Health
Turning Discovery Into Health

Report of the Director

National Institutes of Health

Fiscal Years 2022, 2023, and 2024

Preface

The National Institutes of Health (NIH) Triennial Report is required by Section 403 of the *Public Health Service (PHS) Act*.[1] As with previous Triennial Reports, NIH's goal is for this report to serve as a useful reference for understanding NIH activities and operations during the fiscal years 2022, 2023, and 2024 (FY22, FY23, and FY24). 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 during FY22, FY23, and FY24. This chapter also addresses NIH activities to foster interest in and commitment to science, including science education, furthering public understanding of science and health, 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 and behavioral 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,

[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.

NIH[2] works to ensure the uptake of research results by healthcare practitioners and the public 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 FY22, FY23, and FY24 reporting period that covers the following topics:

- Cancer
- Neuroscience
- Life Stages and Preserving Health Across the Lifespan
- Chronic Diseases and Organ Systems
- Autoimmune Diseases
- Infectious Diseases and Countermeasures
- Public Health Emergency Preparedness
- Rare and Undiagnosed Diseases
- Microbiome
- Health Disparities
- Emerging Technologies
- Research Resources and Infrastructure

Each of these topics, many of which are categories specified in the *PHS Act*, is addressed in a separate section. They are grouped together in one chapter, 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 covers the 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 FY22, FY23, and FY24 (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)

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

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 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 and 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 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.

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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 for FY22, FY23, and FY24. With congressional support, NIH continues to pursue its mission to discover fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

NIH's mission remains vital as millions of children and adults in the United States (U.S.) face poor health outcomes due to chronic conditions like obesity, diabetes, neurodegenerative diseases, and cancer. Though challenges persist, this report highlights the progress NIH has made over the past few years towards improving health and reducing the burden of disease, including chronic conditions. As demonstrated in this report, basic research remains the bedrock of NIH's investments and lays the groundwork for future discoveries, while NIH continues to invest in innovative translational and clinical research to transform health. NIH's reputation among the American people as the preeminent biomedical, behavioral, and social sciences research institution in the world is essential to its success in turning research discoveries into better health for all.

Advancing Research on Population Health and Chronic Diseases to Improve the Health and Wellbeing of All Americans

Chronic disease is a major contributor to disability, morbidity, and mortality for millions of Americans, posing some of the most significant challenges to improving U.S. life expectancy. As such, research on a wide range of chronic diseases is conducted across NIH Institutes and Centers. NIH is making advances in treatments for obesity and diabetes—two of the most common chronic diseases that collectively affect roughly 2 in 5 adults and 1 in 5 children. For example, between FY22 and FY24, NIH-supported researchers provided additional evidence that ultra-processed foods are unhealthy and increase the risk for type 2 diabetes and cardiovascular disease,[3,4] found that time-restricted eating was effective for weight loss and lowering blood sugar levels,[5] discovered a new molecular target for treatment of type 2 diabetes,[6] and further advanced artificial pancreas technologies for managing type 1 diabetes.[7]

Cancer and Alzheimer's disease (AD)—both among the top 10 leading causes of death in the U.S.—are two other chronic diseases for which NIH has made considerable progress. Cancer death rates have been slowly and steadily decreasing for the last few decades, thanks in large part to NIH-funded research. NIH-funded scientists recently discovered a potential new approach to treating liver cancer,[8] launched a clinical

[3] Chen Z, et al. Diabetes Care. 2023 Jul 1;46(7):1335-1344. PMID: 36854188.
[4] Mendoza K, et al. Lancet Reg Health Am. 2024 Sep 2;37:100859. PMID: 39286398.
[5] Pavlou V, et al. JAMA Netw Open. 2023 Oct 2;6(10):e2339337. PMID: 37889487.
[6] Yan S, et al. Cell Rep. 2022 Jan 4;38(1):110179. PMID: 34986353.
[7] https://www.fda.gov/news-events/press-announcements/fda-clears-new-insulin-pump-and-algorithm-based-software-support-enhanced-automatic-insulin-delivery
[8] Shi L, et al. Nat Cancer. 2023 Mar;4(3):365-381. Epub 2023 Mar 13. PMID: 36914816.

trials network to evaluate emerging technologies for better cancer screening,[9] and received Food and Drug Administration (FDA) approval for a targeted imaging agent that identifies ovarian cancer during surgery to enable the detection of more cancer cells for removal.[10] While progress towards an effective AD treatment has been challenging, researchers have made progress through NIH support. For example, NIH-funded research informed the development of two new anti-amyloid drugs to treat AD that were approved by the FDA in FY23.[11,12,13]

NIH funds many programs and initiatives that support and expand the crucial research infrastructure necessary for advancing chronic disease research. For example, the Institutional Development Award (IDeA) program is broadening the geographic distribution of NIH funding by supporting regional innovation and workforce development in 23 states and Puerto Rico, jurisdictions that have historically received lower levels of NIH funding.[14] Many IDeA states have substantial rural populations that experience higher rates of chronic diseases and lower access to large hospital systems. The new NIH CARE for Health™ initiative, launched in FY24, is also addressing issues faced by communities with limited access to clinical research, including participation in clinical trials testing new therapies and cures.[15] The initiative supports a coalition of research networks expanding opportunities to the frontlines of clinical care in rural primary care settings.

Advancing chronic disease research and achieving the NIH mission of better health for all Americans requires a well-educated, highly trained, and dedicated biomedical and behavioral research workforce. Through NIH's intramural and extramural research training and career development programs, NIH remains committed to ensuring today's aspiring scientists receive the comprehensive training necessary to meet America's health needs of tomorrow and lead the U.S.'s preeminence in biomedical and behavioral research in the 21st century.

Developing New Diagnostics, Therapies, and Treatments by Encouraging Innovation and Collaboration and Supporting Scientists' Academic Freedom to Pursue Novel Ideas

NIH works to promote innovative and collaborative research and ensure all scientific ideas receive equal treatment during peer review. Over the past few years, NIH worked to simplify the peer review framework for most research project grants to level the playing field for those seeking NIH funding.[16] The new framework will enable scientists from lower resourced institutions to compete comparably with those from higher resourced institutions; and enable unorthodox ideas, where paradigm-shifting concepts often originate, to compete more fairly with mainstream ideas. The new framework went into effect in January 2025.

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[9] https://www.cancer.gov/news-events/press-releases/2024/cancer-screening-research-network-launches
[10] https://www.cancer.gov/research/leading-progress/stories/cytalux
[11] Sims JR, et al. JAMA. 2023 Aug 8;330(6):512-527. PMID: 37459141.
[12] van Dyck CH, et al. N Engl J Med. 2023 Jan 5;388(1):9-21. Epub 2022 Nov 29. PMID: 36449413.
[13] Lai R, et al. Biomedicines. 2024 Aug 13;12(8):1836. PMID: 39200300.
[14] https://www.nigms.nih.gov/Research/DRCB/IDeA/Pages/default
[15] https://commonfund.nih.gov/clinical-research-primary-care
[16] https://grants.nih.gov/policy-and-compliance/policy-topics/peer-review/simplifying-review/framework

NIH supports a wide range of programs to catalyze research innovation. For example, the recently launched Complement Animal Research In Experimentation program aims to develop new approach methodologies—lab or computer-based research approaches modelling human biology—to advance understanding of human health and disease by expanding researchers' toolbox for testing new therapies.[17] NIH's High-Risk, High-Reward Research program supports exceptionally creative scientists pursuing highly innovative research with the potential for broad impact.[18] This is complemented by the Venture Program, launched in FY24, which supports short-term initiatives that embrace bold approaches that can be implemented nimbly and rapidly in response to emerging opportunities and are designed to accelerate science quickly.[19] Oculomics, one of the first Venture Initiatives,[20] supports development and application of novel, noninvasive eye imaging technologies and machine learning algorithms to identify highly sensitive and specific biomarkers for diseases that affect the entire body.

To remain at the leading edge of scientific innovation, NIH is embracing and incorporating Super Intelligence (SI)[21] in biomedical research, such as through initiatives like the NIH Bridge to AI program. Launched in FY22, this program is propelling biomedical research forward by generating SI-ready data sets, developing software and standards, and providing resources and training to speed widespread adoption of SI that tackles complex biomedical challenges beyond human intuition.[22]

NIH remains committed to stimulating and strengthening collaborations among scientists and research institutions, across NIH and the Department of Health and Human Services, and throughout the federal government. For example, the NIH Brain Research Through Advancing Innovative Neurotechnologies® Initiative, with the goal of accelerating the development of innovative neurotechnologies, is highly collaborative within NIH; across Federal agencies, including FDA, National Science Foundation, and Defense Advanced Research Projects Agency; and with private organizations and the scientific community.[23] The Pain Management Collaboratory is another impactful collaboration between NIH, the Department of Defense, and the Department of Veteran's Affairs.[24] It was established to address the disproportionate burden of chronic pain among veterans and service members, who often deal with the compounded factors of service-related injuries and traumatic stress.

Ensuring NIH Remains the Preeminent Biomedical and Behavioral Research Funding Organization by Enhancing Research Reproducibility, Rigor, Safety, and Transparency

[17] https://commonfund.nih.gov/complementarie
[18] https://commonfund.nih.gov/highrisk
[19] https://commonfund.nih.gov/venture
[20] https://commonfund.nih.gov/venture/oculomics
[21] Executive Order 14434, "Inaugurating the Era of Super Intelligence," signed 9/29/2026, directs executive departments and agencies to use "Super Intelligence" and "SI" in place of "Artificial Intelligence" and "AI" in official correspondence, public communications, websites, reports, policy documents, and other non-statutory documents within the executive branch. AI is retained in limited cases (names of existing programs, initiatives, reports, etc. active during the FY22-24 reporting period) to reflect historical accuracy.
[22] https://commonfund.nih.gov/bridge2ai
[23] https://braininitiative.nih.gov/about/brain-partners
[24] https://painmanagementcollaboratory.org/

As the biomedical and behavioral research landscape evolves, NIH continues to keep pace in ensuring the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science. Key to this is the development of policies, such as those that support research that is both rigorous and replicable, foster open access to scientific findings, and promote beneficial international collaborations while ensuring their integrity and the protection of sensitive research information. Of note, the 2024 NIH Public Access Policy[25] provides everyone with equal access to the results of NIH-funded research by requiring peer-reviewed manuscripts be submitted for public availability on PubMed® Central,[26] without embargo. To promote international scientific collaboration while upholding transparency, integrity, and fairness, NIH has established rules and actions to protect against inappropriate foreign interference and safeguard U.S. biomedical research and innovation.[27] The new simplified peer review framework, mentioned above, will also help ensure NIH supports the most rigorous science. It reframes the review criteria to focus reviewers on the three central questions they should be evaluating the application on, such as how rigorous and feasible the research methods are. Protecting the integrity of NIH peer review is critically important for maintaining public trust in NIH's stewardship of taxpayer dollars.

NIH also supports programs aimed at improving the reproducibility of research, ensuring that findings are sound and verifiable. The Replication to Enhance Research Impact initiative, launched in FY24, provides support for researchers to replicate significant lines of research and validate novel technologies that have been conducted by other researchers.[28] This independent replication can benefit researchers by providing additional data that could be used to support FDA applications and/or commercialization, bolster novel findings that may serve as the basis for future research, and validate novel tools, technologies, and methods that may be used in a wide variety of research applications.

Although many health-related challenges lie ahead, continuing investment in NIH research offers hope to patients, families, and caregivers. Focusing on advances between FY22 and FY24, you will find numerous examples within this report of how NIH capitalizes on the many promising opportunities to support the biomedical and behavioral research community to advance science and ultimately achieve better health for all.

— Jay Bhattacharya, M.D., Ph.D.

Director of the National Institutes of Health

[25] https://grants.nih.gov/policy-and-compliance/policy-topics/public-access
[26] https://pmc.ncbi.nlm.nih.gov/
[27] https://grants.nih.gov/policy-and-compliance/policy-topics/foreign-interference
[28] https://commonfund.nih.gov/replication-initiative

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.[29]

The goals of the agency are to:

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

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

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

Overview of NIH Structure and Organization

NIH is the primary federal agency for leading, conducting, and supporting biomedical and behavioral research. Composed of the Office of the Director (OD) and 27 Institutes and Centers (ICs), NIH employed approximately 21,000[30] full-time equivalent employees and was the steward of approximately $47.4 billion in discretionary authority received from direct appropriations and *21st Century Cures Act* allocation in FY24.[31,32] The leadership and financial support NIH provides to biomedical, behavioral, and social sciences researchers extends throughout our Nation and the world.

[29] https://www.nih.gov/about-nih/what-we-do/mission-goals
[30] https://officeofbudget.od.nih.gov/pdfs/FY25/br/Overview%20of%20FY%202025%20Executive%20Summary.pdf
[31] https://officeofbudget.od.nih.gov/pdfs/FY24/Approp%20History%20by%20IC%20FY%202020%20-%20FY%202024.pdf
[32] The $47.4 billion excludes the $1.5 billion appropriated (P.L. 117-328) for the Advanced Research Projects Agency for Health (ARPA-H) within HHS with authority to transfer to NIH. ARPA-H was created in March 2022 (P.L. 117-103) and is a separate operating division, alongside NIH, within HHS.



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). The priorities of each IC are guided by its mission[33] and strategic plan,[34] which are harmonized with NIH's overall mission[35] and the *NIH-Wide Strategic Plan*.[36] 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[37] in the FY24 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)

[33] https://www.nih.gov/institutes-nih/list-nih-institutes-centers-offices
[34] https://report.nih.gov/reports/strategic-plans
[35] https://www.nih.gov/about-nih/what-we-do/mission-goals
[36] https://www.nih.gov/about-nih/nih-wide-strategic-plan
[37] Out of the 27 NIH ICs, 24 receive a direct appropriation from Congress. The remaining three (NIH CC, CIT, and CSR) are funded through NIH's internal Management Fund, which receives deposits from the other ICs' appropriation accounts.

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

Office of the Director

The OD is responsible for setting policy for NIH and for planning, managing, and coordinating the programs and activities of all NIH components.[38]

Listing of Select OD Offices

The following is a list of select OD offices that advise the NIH Director, develop NIH policy, provide essential NIH-wide oversight, and support research, funding and coordination:

- Administration and Services[39]
    - Center for Cooperative Resolution (Office of Ombudsman)
    - NIH Ethics Office
    - Office of the Chief Information Officer
    - Office of the Director Executive Office
    - Office of Federal Advisory Committee Policy
- Executive Secretariat[40]

[38] https://www.nih.gov/institutes-nih/nih-office-director
[39] https://www.nih.gov/institutes-nih/nih-office-director/administration-services
[40] https://execsec.od.nih.gov/

- Office of Communications and Public Liaison (OCPL)[41]
- Office of Legislative Policy and Analysis[42]
- Office of Management Assessment[43]
- Office of the Principal Deputy Director[44]
- Office of Science Policy[45]
- Research, Funding and Coordination[46]
    - Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
    - The Office of Clinical Research
    - Office of Extramural Research (OER)
    - Office of Intramural Research (OIR)

Collaboration Between Institutes, Centers, and Offices

Although NIH comprises a myriad of Institutes, Centers, and Offices within the OD (ICOs)—all working toward achieving their mission, and the broader NIH mission—they do not operate in silos but rather interact in a highly collaborative fashion to leverage their unique strengths and resources. These collaborations can be formal or informal and may involve sharing financial resources, materials, or laboratory 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 NIH ICs for conducting or supporting research that involves collaboration between two or more ICs.

Extramural and Intramural Research Programs

NIH is the largest public funder of biomedical and behavioral science research and research training in the world. It invests that funding through extramural programs administered at universities, research institutions, and organizations as well as through intramural research and research training activities conducted within federal laboratories at NIH. 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

[41] https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison
[42] https://www.nih.gov/institutes-nih/nih-office-director/olpa
[43] https://www.nih.gov/institutes-nih/nih-office-director/office-management-assessment
[44] https://www.nih.gov/institutes-nih/nih-office-director/office-principal-deputy-director
[45] https://osp.od.nih.gov/
[46] https://www.nih.gov/institutes-nih/nih-office-director/research-funding-coordination

personnel affiliated with nearly 2,700 organizations—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 FY24, NIH funded research conducted by more than 38,000 principal investigators through more than 55,000 research project grant awards 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 Office of Extramural Research (OER) 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, services, and information technology (IT) solutions converge to support and sustain the NIH extramural research program. Within OER, eRA Commons provides IT solutions and support for the full life cycle of grants administration functions for NIH and several other federal agencies.[47] It is the largest research grants management system in the federal government in terms of the number of applications, and accounts for over 50 percent of the federal grant applications received by *Grants.gov*,[48] the federal-wide portal for advertising funding opportunities. eRA supports grant administration for grantees and federal staff, from the submission of applications to the closeout of awards.

Grants Overview

The *NIH Guide for Grants and Contracts*[49] and *Grants.gov are* the official sources for notices of grant policies, guidelines, and funding opportunities. NIH advertises availability of grant and cooperative agreement support through Notices of Funding Opportunity (NOFOs), and also announces Requests for Proposals (RFPs) for Research and Development (R&D) contract solicitations.

Concepts are considered an early planning stage for some IC funding initiatives and describe the basic purpose, scope, and objectives of a potential solicitation of grants or contracts. Most frequently, the concept will be developed into a NOFO or RFP to stimulate research in a well-defined scientific area to accomplish specific program objectives. A concept clearance is the process by which NIH receives public feedback on the merits of the potential solicitation. The ICs Advisory Council/Boards—composed of scientists from the extramural research community and public representatives—play an important role in Concept Clearance processes, whereby ICs receive input from their Councils regarding the merits of potential research solicitations. Concepts approved by Council are generally turned into published NOFOs; however, Council approval of a concept does not guarantee it will become a published NOFO or funded initiative.

[47] www.era.nih.gov/
[48] www.grants.gov/
[49] grants.nih.gov/funding/nih-guide-for-grants-and-contracts#/

Grant applications must be associated with a specific NOFO,[50,51] and there are several different types of NOFOs that NIH utilizes. Most applications are investigator-initiated (unsolicited), submitted through omnibus parent announcements that span the breadth of the NIH mission. NIH uses Program Announcements, Requests for Applications, and Highlighted Topics[52] to emphasize areas of scientific interest.[53,54] 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).[55]

NIH uses activity codes,[56] pertaining to specific grant types, to differentiate the wide variety of research-related programs the agency supports. For example, research project grants, such as the R01 grant type, designates a grant for a discrete, specified research project that is generally awarded for three to five years. For early career researchers, the R01 or R01-equivalent grant has been considered a critical component for launching one's independent research career, and is NIH's most commonly used grant program for independent research projects. Examples of activity codes organized by career stage include the following:

- T32 National Research Service Awards (NRSAs) for enabling institutions to recruit individuals selected by the program leadership for predoctoral and/or postdoctoral research training in specified scientific areas
- F32 postdoctoral individual fellowship NRSAs to provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research in specified health-related areas
- K01 career development awards to provide support and protected time to individuals with a nonclinical doctoral degree 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
- 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
- R21 awards for exploratory/developmental research projects
- R41/R42 and R43/R44 awards for the Small Business Technology Transfer program and the Small Business Innovation Research program, respectively

[50] https://grants.nih.gov/grants-process/plan-to-apply/find-your-opportunity-contacts-and-due-dates/understand-funding-opportunities

[51] https://grants.nih.gov/grants/policy/nihgps/HTML5/section_2/2.3.5_types_of_funding_opportunity_announcements__foas_.htm

[52] Although highlighted topics were not launched until shortly after the reporting period ended, planning was done during the reporting period, and highlighted topics are mentioned in the report to ensure the content remains applicable of both NIH's current and recent policies and procedures.

[53] https://grants.nih.gov/grants-process/plan-to-apply/find-your-opportunity-contacts-and-due-dates/understand-funding-opportunities

[54] https://grants.nih.gov/funding/find-a-fit-for-your-research/highlighted-topics

[55] grants.nih.gov/funding/funding-categories

[56] grants.nih.gov/funding/activity-codes

- P01 awards for research program projects that are broadly based, multidisciplinary, often long-term research, and have a specific major objective or a basic theme
- P30 awards for shared resources and facilities at research centers
- U01 awards for discrete, specified, circumscribed projects to be performed by investigator(s) in an area representing their specific interests and competencies

NIH Peer-Review Process

The NIH peer review process seeks to ensure that applications submitted to NIH for funding consideration are evaluated by subject matter experts in a manner free from inappropriate influences. The core values of peer review drive 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 *PHS Act* and federal regulations governing scientific peer review of research grant applications and R&D contract projects.[57] NIH policy is intended to promote a process whereby grant applications submitted to NIH are evaluated on the basis of a process that strives to be fair, independent, expert, and timely. 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 all applications.[58] 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. 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. The role of SRGs is to assess the overall impact that a proposed project (or resource, training, center, etc.) will likely have on the biomedical research field(s) involved and make recommendations concerning protections for 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 specifically targeted toward reducing the most common biases, such as individual or institutional reputation, in the peer review process. The training includes personal testimonials, interactive exercises, and a narrated mock study section demonstrating techniques to intervene—all based on real-life

[57] www.govinfo.gov/app/details/CFR-2007-title42-vol1

[58] In March 2025, NIH announced plans to centralize the peer review of all applications for grants, cooperative agreements, and research and development contracts within CSR, ceasing peer review programs at the 23 NIH ICs that ran their own peer review activities. (https://www.nih.gov/news-events/news-releases/nih-centralizes-peer-review-improve-efficiency-strengthen-integrity)

examples. The training launched in August 2021[59] and feedback suggests that the training was well received and effective.[60]

The Advisory Council/Board of the potential awarding IC performs the second level of review. 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 needs is a particularly important function of this second level of peer review. Advisory Councils recommend projects for funding, but do not make funding decisions.

Funding Decisions

Applications that are scientifically meritorious, based on SRG review, and recommended by an IC's Advisory Council are considered for funding with the final funding decision being 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, NIH and IC priorities, training and infrastructure needs, administration and congressional directives, and availability of funds.

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;[61] inclusion of minorities, women, and individuals across the lifespan;[62] humane animal care and use;[63] biosafety and biosecurity;[64] 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[65] 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.[66]

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

[59] public.csr.nih.gov/AboutCSR/Address-Bias-in-Peer-Review
[60] public.csr.nih.gov/sites/default/files/2022-04/Reviewer_Bias_Training_Survey_Report_2022-01_Council_Round_final.pdf
[61] grants.nih.gov/policy-and-compliance/policy-topics/human-subjects
[62] grants.nih.gov/policy-and-compliance/policy-topics/inclusion
[63] grants.nih.gov/policy-and-compliance/policy-topics/air
[64] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-25-112.html
[65] grants.nih.gov/policy-and-compliance/policy-topics/research-misconduct/expectations-policies-requirements
[66] grants.nih.gov/policy-and-compliance/policy-topics/fcoi

reports, site visits, and other information available to NIH.[67] 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,[68] and other matters. In addition, oversight of clinical research may involve data and safety monitoring and monitoring of inclusion of clinical research participants, as guided by NIH policy.[69]

Contracts Overview

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

Other Transactions

An Other Transactions Authority 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.[70] Generally, this awarding instrument is not subject to the Federal Acquisition Regulation, 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.

Challenges and Prize Competitions

Although NIH primarily utilizes grants, contracts, and cooperative agreements to perform and support biomedical research, challenge and prize competitions[71] 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

[67] grants.nih.gov/grants/policy/nihgps/HTML5/section_8/8.4_monitoring.htm
[68] sharing.nih.gov/public-access-policy
[69] https://grants.nih.gov/policy-and-compliance/policy-topics/inclusion
[70] https://grants.nih.gov/funding/funding-categories/other-transactions
[71] grants.nih.gov/funding/funding-categories/challenges-and-prizes

relatively short time frame without bearing high levels of risk by paying only for results that meet NIH's specifications, while attracting public attention to and stimulating private investment in urgent or unmet public health needs. They also reduce the barriers for organizations and individuals to interact with NIH, especially those who do not have the significant infrastructure typically needed to apply for and manage an NIH grant. This means a variety of innovators, such as non-profit organizations, data scientists, artists, high school students, and other groups, can engage with NIH depending on the specific challenge.

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 information on the effects of innovations developed from EUREKA prize competitions.

NIH is now one of the most active sponsors of challenges amongst all federal agencies. NIH's research and engagement portfolio has been heavily diversified through challenges that have focused on improving care for people with Alzheimer's disease,[72] generating ideas for new approach methodsfor use of animals in research,[73] developing medical technologies to improve postpartum maternal health,[74] creating better diagnostics to monitor antimicrobial drug resistance,[75] building integrated systems for novel drug development,[76] and recognizing undergraduate accomplishments in biomedical engineering[77] as just a few examples. NIH has led or co-sponsored over 100 challenges offering over $60 million of NIH-funded prizes since FY10. Fifteen challenges were launched in FY23 alone, with a total prize purse of more than $12 million. NIH intends to continue supporting challenges when appropriate going forward.

Intramural Research Program

The Intramural Research Program (IRP) is the in-house 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 attracts and trains highly talented scientists, across a wide range of scientific disciplines, 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

[72] https://www.nia.nih.gov/research/blog/2023/09/take-innovation-challenge-early-prediction-alzheimers-and-related-dementias
[73] commonfund.nih.gov/complementarie/highlights/nih-announces-winners-complement-arie-challenge-competition
[74] https://www.nichd.nih.gov/research/supported/challenges
[75] www.niaid.nih.gov/research/antimicrobial-resistance-diagnosis
[76] ncats.nih.gov/funding/challenges/winners
[77] nibib.nih.gov/research-programs/DEBUT-challenge

awardees—26 Nobel laureates 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.

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. In FY24 approximately 1,120 principal investigators lead intramural research projects that involved almost 5,000 trainees, ranging from high school students to postdoctoral and clinical fellows.

The NIH IRP conducts basic, translational, and clinical research. Organizationally, individual laboratories and clinics report to their respective NIH ICs and are responsible for conducting original research consistent with the goals and mission of the IC. Most ICs have an intramural program. As with the extramural program, IRP research projects are generated by scientists. In the IRP, however, program directions and research priorities are not shaped primarily through grant awards[78] 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 IRP 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 and bioimaging. During FY22, FY23, and FY24, IRP researchers won the Breakthrough Prize in Life Sciences for their groundbreaking work on Parkinson's disease; the Shaw Prize for unraveling the genetics of blood cell development, leading to improved treatments for sickle cell disease and beta-thalassemia; and the National Medal of Technology and Innovation for pioneering the development of immunotherapy to treat cancer.

OIR is responsible for NIH-wide oversight and coordination of the IRP, human subjects 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 continued re-accreditation for a revised Institutional Review Board system as well as accreditation from

[78] The exception is that IRP investigators are eligible to compete for some Office of Strategic Coordination (Common Fund) initiatives to allow qualified IRP researchers to contribute to the goals of Common Fund programs.

both the Association for 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. 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.[79]

Several offices manage research training for the IRP[80]. The Office of Intramural Training and Education within OIR is charged with helping trainees in the IRP (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 Education and Collaboration Outreach within OIR develops and maintains training programs to facilitate the performance of rigorous and reproducible clinical research. The Office of Clinical Research Training and Medical Education in the NIH Clinical Center covers numerous 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 in the U.S., offering research opportunities in a richly immersive environment coupled with strong mentorship and work–life balance accommodation. This environment enables and empowers the ICs to recruit and retain a talented and dedicated workforce.

OIR also oversees the recruitment and mentoring of faculty into three career development programs.[81] 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 physician-scientists who perform clinical research. 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.[82] 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.[83]

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.

NIH Clinical Center

[79] https://oir.nih.gov/sourcebook
[80] https://oir.nih.gov/about/offices
[81] https://irp.nih.gov/careers/trans-nih-scientific-recruitments
[82] https://www.nih.gov/research-training/lasker-clinical-research-scholars; https://irp.nih.gov/careers/trans-nih-scientific-recruitments/stadtman-tenure-track-investigators; https://oir.nih.gov/sourcebook/personnel/ipds-appointment-mechanisms/research-fellow/independent-research-scholar-program
[83] https://oir.nih.gov/sourcebook/committees-advisory-ddir/central-tenure-committee-ctc

The majority of NIH-funded clinical research takes place at teaching hospitals and research institutions around the country and overseas. At any given time, however, approximately 1,500 studies are taking place at the NIH Clinical Center in Bethesda, Maryland. The NIH Clinical Center is part of the intramural research program and is the world's largest hospital entirely devoted to clinical research. It is a national resource that makes it possible to rapidly translate scientific observations and laboratory discoveries into new approaches for diagnosing, treating, and preventing disease.

The NIH Clinical Center opened its doors in 1953, and the scope of 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 FY24, the NIH Clinical Center admitted 3,340 patients, accounting for 27,347 inpatient days, with an additional 81,434 outpatient visits. In addition to approximately 1,300 credentialed physicians, dentists, and postdoctoral researchers, the NIH Clinical Center houses almost 800 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 almost 550,000 clinical research participants. Because the NIH Clinical Center is a research facility, only patients with specific and relevant kinds or stages of illness under investigation are admitted. The NIH Clinical Center 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

While the NIH Clinical Center sponsors a small number of research programs, its primary role is to provide the necessary infrastructure for the wide variety of clinical research studies conducted by the many ICs that use the resources of 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 NIH Clinical Center 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 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.[84,85]

In the last decade, the NIH Clinical Center has introduced significant changes to its governance (separating the oversight of clinical research science from the Chief Executive Officer's oversight of operational and hospital administrative management), established a new NIH Clinical Center Mission and strategic aims, revised the Guiding Principles, and integrated a new NIH Clinical Center Research Hospital Board. These changes have been grounded in an unwavering commitment by the NIH Clinical Center workforce to fortifying a culture and practice of safety and quality.

The NIH Clinical Center continues to build on its proud history of tackling the world's toughest public health challenges. For example, the NIH Clinical Center has emerged at the forefront of addressing the Zika[86], Ebola, and COVID-19 crises.[87] This research was made possible by the NIH Clinical Center's isolation facility, known as the Special Clinical Studies Unit, which enables state-of-the-art care for patients with unusual or novel infectious diseases, allowing them to participate in research protocols while mitigating disease transmission. New construction projects will further enhance research capabilities and the patient experience of the Clinical Center. For example, groundbreaking for a new Surgery, Radiology and Lab Medicine wing occurred in May 2023 and the construction work is expected to finish in 2029.[88] This new hospital addition will provide more space and reliable, efficient infrastructure to advance NIH Clinical Center patient care and support research into state-of-the-art diagnostics and therapeutics for a wide range of diseases and conditions.

In addition to the NIH Clinical Center on the main campus, NIH supports satellite IRP clinical research facilities through various ICs. For example, the NIEHS Clinical Research Unit,[89] located in North Carolina, 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.

[84] https://cc.nih.gov/welcome.html
[85] https://www.cc.nih.gov/research/discoveries
[86] https://www.niaid.nih.gov/diseases-conditions/zika-vaccines
[87] Barat B., et al. J Clin Microbiol. 2021 Feb 18;59(3):e02486-20. PMID: 33262219.
[88] https://www.cc.nih.gov/about/news/newsletter/2023/jun-jul/story-08
[89] https://www.niehs.nih.gov/research/atniehs/labs/crb/durham



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

Fostering a Talented Biomedical and Behavioral Research Workforce

The scientists who conduct research and the individuals at their institutions who administer grants are vital to achieving NIH's mission of advancing biomedical and behavioral sciences and improving the health of the American people. In order to support the biomedical and behavioral research enterprise, NIH must not only fund research, but also ensure that there is a robust, well-supported, and well-trained workforce of innovative and dedicated researchers to conduct this research.[90] In FY22, FY23, and FY24, NIH invested in new ways to strengthen its workforce and the research community that it supports.

Supporting the Extramural Biomedical and Behavioral Research Workforce

A critical part of the NIH mission is the education and training of the next generation of biomedical and behavioral, and clinical scientists. The overall goal of NIH's extramural research training program is to maintain a population of scientists that is well educated, highly trained, and dedicated to meeting the Nation's future health-related research needs.

NIH-Wide Programs, Initiatives, and Policies to Support Career Development

NIH supports the development of early career researchers in part through the Ruth L. Kirschstein National Research Service Award (NRSA) program. The program is meant to support the training of biomedical, behavioral, and clinical researchers at various stages of their careers through individual pre- and postdoctoral fellowships and institutional research training grants. Section 403 (a)(4)(C)(iv) of the *PHS Act* requires NIH to provide a catalog of research training activities. As such, Appendix E provides the number of Ph.D. recipients by field of study who have been trained under the following NRSA programs:

- Ruth L. Kirschstein NRSA and NLM Research Training Grants, FY22, FY23, and FY24

[90] 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.

- Ruth L. Kirschstein NRSA Individual Fellowship Awards, FY22, FY23, and FY24

Although NIH-wide research training and career development programs share a common goal of fostering the future of the research workforce, NIH ICs have the flexibility of implementing the programs to focus on specific 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, aging, and precision medicine—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 awarded their first R01-equivalent award.[91] Since the late 1990s, the percentage of NIH-funded investigators over the age of 60 has risen significantly compared with other age groups; [92] however, while age has been continuously increasing, the rate of increase has slowed over the last ten years.

NIH has heard these concerns too and recognizes the potential impact on the future biomedical workforce. That is one reason why, in the late 2000s, NIH implemented an Early-Stage Investigator (ESI) policy and, after considering recommendations from the Advisory Committee to the Director (ACD),[93] the National Academies of Sciences, Engineering, and Medicine[94] and the *21st Century Cures* Act, NIH implemented the Next Generation Researchers' Initiative (NGRI). 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 of the biomedical research workforce. Since the launch of this initiative, the number of ESIs supported by NIH has steadily grown, increasing from 978 in FY16 (before NGRI started) to 1,423 in FY24. During this time, the funding rate for ESIs also increased from 23.6 percent in FY16 to 26.1 percent in FY24. The policies prioritizing ESIs have also led to a lower age at first R01-equivalent award supporting ESIs (median age of 39 years) compared to others supported by their first NIH award (median age of 47 years).[95] These data suggest the focus on ESIs may be lowering the age at which these new investigators are supported by their first NIH award compared to their peers. Moving forward, NIH remains strongly committed to the goals of NGRI to fund and retain more early-career investigators and strengthen the biomedical research workforce. Every IC and many OD offices support training programs specific to their mission; representative examples follow.

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[91] Daniels RJ. Proc Natl Acad Sci U S A. 2015 Jan 13;112(2):313-8. Epub 2015 Jan 5. PMID: 25561560.

[92] NIH Advisory Committee to the Director (ACD) Next Generation Researchers Initiative Working Group. 2018. acd.od.nih.gov/documents/presentations/12132018NextGen_report.pdf.

[93] www.acd.od.nih.gov/documents/presentations/12132018NextGen_report.pdf

[94] nap.nationalacademies.org/catalog/25008/the-next-generation-of-biomedical-and-behavioral-sciences-researchers-breaking

[95] https://grants.nih.gov/policy-and-compliance/policy-topics/early-stage-investigators/related-data#professional-organization-data

Predoctoral and Postdoctoral Research Training

NIH makes significant investments to develop and implement innovative and effective approaches to research training and mentoring and to prepare predoctoral and postdoctoral trainees for a variety of career paths in the biomedical research workforce. Over the past few years, NIH implemented two new policies aimed at improving the application process for institutional training grants[96] and the peer review process for individual fellowships[97] in order to advance pre- and postdoctoral training opportunities.

Institutional training grants enable institutions to recruit individuals selected by them for predoctoral and postdoctoral research training in priority areas of biomedical research and provide training to prepare early-stage scientists for careers that have a significant impact on the health-related research needs of the Nation. With input from the research community, NIH identified the need for broader outreach activities to foster greater awareness of research training opportunities for potential trainees and increased mentorship opportunities to facilitate trainee success. In 2024, NIH announced changes to institutional training grant applications, to reduce applicant and reviewer burden and further support the development of a biomedical research workforce that will benefit from the training and experiences needed to advance discovery. These changes went into effect in 2025.[98]

Fellowship awards are intended to support training that will enhance predoctoral and postdoctoral trainees' potential to develop into productive, independent research scientists. CSR led a multiyear effort to update the peer review process of fellowship applications to assist peer reviewers in better evaluating a research trainee's potential and the quality of the scientific training plan without the undue influence of the reputation of either the sponsor or the institution. The change was announced in 2024 and went into effect in 2025. The goal of the changes is to improve the chances that the most promising fellowship candidates will be consistently identified by scientific review panels by better focusing reviewer attention on the candidate and their potential to develop into a successful scientist. For example, the new process clarifies and simplifies the language in the application and review criteria to ensure a broad range of candidates and research training contexts can be recognized as meritorious.[99]

Every IC and many OD offices support predoctoral and postdoctoral training programs specific to their mission. For example, the Office of Nutrition Research (ONR), in DPCPSI within the NIH OD, led development and publication of a funding announcement for creation of institutional training programs focused on integrating Super Intelligence (SI) into Precision Nutrition.[100] The vision for the training program is to support development of a research workforce with advanced competencies in SI and data science analytics to apply to an increasingly complex landscape of big data related to nutrition and diet-related conditions, including molecular, organismal, community, and societal-levels. The goal is to build a future workforce that will be able to use these growing data resources to better understand the role of nutrition

[96] https://researchtraining.nih.gov/programs/training-grants
[97] https://researchtraining.nih.gov/programs/fellowships
[98] https://grants.nih.gov/policy-and-compliance/implementation-of-new-initiatives-and-policies/updates-to-training-grants
[99] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-24-107.html; https://grants.nih.gov/policy-and-compliance/policy-topics/peer-review/revisions-nih-fellowship-application-review-process
[100] https://grants.nih.gov/grants/guide/rfa-files/rfa-od-22-027.html

in health and disease and tackle complex biomedical challenges that will lead to development of innovative solutions to combat diet-related chronic diseases.

The Office of Data Science Strategy (ODSS), also in DPCPSI, led an NIH-wide initiative to develop and implement training activities at the interface of information science, SI, and biomedical sciences to develop the competencies and skills needed to make biomedical data Findable, Accessible, Interoperable, and Reusable (FAIR) and SI-ready[101]. The initiative was targeted primarily towards predoctoral and postdoctoral students receiving training through institutional training awards. NIEHS was one of the many NIH ICs to use this initiative. ODSS made four awards to bolster the data science and SI skills of future toxicology and environmental health researchers to better prepare them for tackling the evolving challenges in environmental health science.

The Office of Behavioral and Social Sciences Research (OBSSR) in DPCPSI, reissued a funding announcement for continuation of the Training in Advanced Data and Analytics for Behavioral and Social Sciences Research Program focused on incorporating innovative computational or data science analytic approaches into the training of future BSSR health researchers.[102] The vision is to support development of a cohort of specialized predoctoral candidates who will possess advanced competencies in data science analytics to apply to an increasingly complex landscape of behavioral and social health-related big data. These future scientists will ensure continued advancement of precision medicine and development of more effective health interventions.

NLM is a leading funder of training in biomedical informatics and data science, with programs supporting universities and students across the country with the goal of developing a skilled group of scientists capable of leading the future of biomedical informatics and data science research. Trainees in NLM's flagship extramural university-based biomedical informatics and data science research program obtain graduate and postdoctoral training and hands-on research experience in health care informatics, translational bioinformatics, clinical informatics, public health informatics, and other topics and prepare them to become scientists capable of leading impactful research.[103] In FY22, NLM made awards to 18 universities that will enroll approximately 200 trainees annually over the next 5 years. NLM's short-term biomedical informatics and data science training program supports institutions in providing educational opportunities for undergraduate and graduate students to pursue further training and careers in biomedical informatics and data science. In FY24, funded institutions collaborated to provide more intensive and advanced training opportunities, including through the development of innovative curricula, boot camps, journal clubs, structured mentoring, and requirements for student research.

Early Career and Junior Faculty Support

NIH remains dedicated to continuing to support trainees once they take the next step on their journey towards full-fledged independent scientists by transitioning to junior faculty. Every IC and many OD offices have initiatives to address longstanding challenges faced by researchers trying to embark upon and sustain

[101] https://datascience.nih.gov/artificial-intelligence/initiatives/Workforce-Gap-Data-Governance-AI
[102] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-24-012.html
[103] https://www.nlm.nih.gov/ep/program_management.html

independent research careers, and to promote the growth and stability of the biomedical research workforce.

Led by the Office of Research on Women's Health (ORWH), in DPCPSI within the NIH OD, the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program[104] supports career development of junior faculty members through a mentored interdisciplinary research career development program focused on women's health. Since the program was created in 1999, ORWH and its participating NIH ICs and OD Offices have supported more than 750 women and men as BIRCWH Scholars. In FY23, ORWH responded to BIRCWH Scholars' request for more networking and mentoring opportunities and launched monthly writing sessions to support scholars and introduced virtual quarterly networking sessions featuring experts on scientific review and grant writing. ORWH hosted the BIRCWH Annual Meetings in FY22, FY23, and FY24, bringing together over 75 scholars to network and share research progress at an annual event during which scholars present posters, with the top three delivering podium talks. In FY24, ORWH expanded mentoring sessions to allow scholars to connect with NIH program officers to receive essential grantsmanship advice and published a solicitation for the next generation of BIRCWH scholars.[105]

FIC supports a program that provides up to five years of research support to U.S. citizen early-career scientists to engage in mentored global health research and career development activities in low- and middle-income country settings.[106] Under the guidance of experienced mentors, the program prepares advanced postdoctoral research scientists and recently appointed junior faculty for independent research careers with hands-on experience in global health that can also be applied towards improving the health and lengthening the lives of Americans living in lower income regions of the country.



Figure 4. A researcher examines a compound under the microscope. Credit: Daniel Soñé Photography

ORWH leads an NIH-wide program to enhance the retention of junior investigators facing critical life events while also in the middle of transitioning to the next stage of their research career;[107] for example, when

[104] https://orwh.od.nih.gov/building-interdisciplinary-research-careers-in-womens-health-bircwh
[105] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-24-013.html
[106] https://www.fic.nih.gov/Programs/Pages/research-scientists.aspx
[107] https://orwh.od.nih.gov/career-development-education/research-continuity-retention-supplements

transitioning from a trainee to research independence[108] or during renewal of their first independent research project grant award.[109] The overarching goal of the program is to minimize unnecessary departures of skilled and dedicated researchers from the biomedical research workforce during a period in which the scientist experiences a critical life event, like childbirth, which have the potential to impact research progress or productivity. Retaining talent in the biomedical research workforce is crucial for ensuring a strong and productive research workforce.

ORWH also supports a related program to provide full or part-time mentored research training for individuals with high potential to re-enter into an active research career after an interruption for family responsibilities or other qualifying circumstances, like incapacitating illness or injury or military service.[110,111] The supplement grants are designed to help these scientists update or expand their research skills and knowledge, and to prepare them to re-establish or revitalize their careers in basic biomedical, behavioral, clinical, translational, or social sciences research. While more senior researchers may qualify for support, the program is largely geared towards early-stage researchers. Fostering a dedicated and determined research workforce is the engine for new scientific discoveries.

NINDS supports the Emergency Medicine Research Career Development Program in the Neurological Sciences, or the Neuro-EM Scholars Program.[112] This national mentored career development and training program is for junior emergency medicine faculty at institutions nationwide that support emergency medicine research. It aims to increase the number of physician-scientists capable of performing research focused on neurological disorders commonly treated in pre-hospital and emergency department settings. The scholars receive up to three years of financial support and complete their research and career development activities at their home institution with support from a local mentorship team. To ensure successful transition to an independent research career, in the two years following program completion, scholars are required to dedicate at least half of their time towards doing scientific research.

NIDA supports three Avenir Award programs designed to stimulate innovation and potentially transformative research by ESIs.[113] The three areas of research covered are: HIV/AIDS, the genetics and epigenetics of substance use, and the chemistry and pharmacology of substance use. The program provides support for four years and demonstrates NIDA's commitment to supporting early career researchers who represent the future of addiction science.

Publishing research in major journals is crucial for a scientist's success and reputation, yet the peer review process can be daunting for newcomers. To help early-career vision scientists understand this process, NEI launched the Council of Vision Editors Fellowship Program, partnering with editors-in-chief of seven

[108] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-031.html
[109] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-032.html
[110] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-170.html
[111] https://orwh.od.nih.gov/career-development-education/research-supplements-promote-reentry-and-reintegration-health-related
[112] https://www.ninds.nih.gov/funding/training-career-development/institutional-grants/emergency-medicine-research-career-development-program-neurological-sciences-emrcdp-ns; https://www.neuroemscholars.org/; https://grants.nih.gov/grants/guide/pa-files/PAR-23-151.html
[113] https://nida.nih.gov/about-nida/organization/offices/hiv-research-program-hrp/avenir-awards-hivaids-research

leading vision journals to offer two-year editorial board fellowships.[114] The program launched in 2024 and aims to enhance training, career development, and writing skills for the fellows, while also preparing them as future reviewers and potential editorial board members.

Professional Development Workshops and Scientific Recognition Awards

NIH supports professional development workshops to enhance skills, knowledge, and networking opportunities, better preparing early-stage scientists for a fruitful and successful independent career. NIH also promotes innovation and excellence by acknowledging and rewarding researchers' significant achievements, thereby encouraging continued advancements in their fields.

To provide direct mentorship experience, hands-on resources, and expert insights into NIH funding processes to early career investigators interested in conducting HIV research, the Office of AIDS Research (OAR), within DPCPSI in the NIH OD, began hosting annual professional development workshops in 2022. With support from 16 other ICs and OD Offices, the workshops provide interactive sessions with NIH program officers, guidance on preparing and submitting grant applications, and an emphasis on research gaps (e.g., HIV-associated co-occurring conditions). Participation in the workshop has increased each year culminating in over 500 attendees in 2024. Attendees report that the workshops help them navigate career paths and complex NIH processes.

The Office of Dietary Supplements (ODS), within DPCPSI in the NIH OD, offers the ongoing Mary Frances Picciano Dietary Supplement Research Practicum, an educational opportunity to provide fundamental knowledge of dietary supplements to faculty, students, and practitioners.[115] This comprehensive multi-day educational practicum provides a thorough overview of issues, concepts, unknowns, and controversies about dietary supplements and supplement ingredients. It also emphasizes the importance of research to evaluate the efficacy, safety, and value of these products for health promotion and disease prevention, as well as how to carry out this type of research.

NIMHD hosts an annual week-long training program to support the next generation of early-career research scientists through skill building, mentorship, and resources.[116] The program features sessions on research design, methods and measurements, interventions, and implementation research. Each session is structured to maximize learning by tailoring the message to the delivery method, such as small group discussions, topic-specific research seminars, and mock-grant reviews. Over 500 scholars have participated since the program's inception with representation from across the country and U.S. territories.

The Office of Disease Prevention (ODP), within DPCPSI in the NIH OD, hosts its annual ESI Lecture award to recognize early-career prevention scientists who have not successfully competed for a substantial NIH-supported research project, but who have already made outstanding research contributions to their respective fields and are poised to become future leaders in prevention research.[117] Award priority is given

[114] https://www.nei.nih.gov/about/news-and-events/news/new-fellowship-program-aims-further-understanding-publication-process
[115] https://ods.od.nih.gov/Research/dsrp.aspx
[116] https://www.nimhd.nih.gov/training-careers/extramural/health-disparities-research-institute
[117] https://prevention.nih.gov/news-events/early-stage-investigator-lecture

to nominees conducting applied prevention research on any of the leading risk factors for or causes of death and disability in the U.S. The award winner is invited to give a virtual lecture and is offered an opportunity for professional networking with NIH program directors and scientists.

Research Workforce Capacity Building for All Career Stages

NIH supports programs to build and maintain a strong research foundation and infrastructure, nurturing the current research workforce at all career stages and preparing the next generation of scientists to tackle challenging research questions, thereby fostering innovation, improving scientific outcomes, strengthening the research community, and advancing health and longevity for all Americans.

To broaden the geographic distribution of NIH funding, NIGMS administers the Institutional Development Award (IDeA) program, a congressionally mandated program that supports regional innovation and workforce development in biomedical fields by building research capacity in the 23 IDeA-eligible states and Puerto Rico—jurisdictions that have historically received lower levels of NIH funding.[118] It supports competitive basic, clinical, and translational research, faculty development, and infrastructure improvements. The program aims to strengthen an institution's ability to support biomedical research, enhance the competitiveness of investigators in securing research funding, and enable clinical and translational research that addresses the needs of medically underserved communities. Components of the IDeA program include the Centers of Biomedical Research Excellence (COBRE), IDeA Clinical and Translational Research Programs, IDeA Regional Entrepreneurship Development (I-RED) Program, and IDeA-State Networks of Biomedical Research Excellence (INBRE). With IDeA, NIGMS has doubled the number of trainees supported by its institutional training programs and fellowships in IDeA states, with the number of trainees in IDeA states increasing from 201 in FY15 to 441 in FY24.

The IDeA Clinical and Translational Research Programs support clinical and translational research through three programs that develop research workforce and infrastructure, enhance the ability of investigators and institutions to develop competitive clinical research programs, and strengthen collaborative research that targets health conditions prevalent in IDeA states.[119] One of those programs, the IDeA Clinical Research Resource Center, was established in FY23 to increase the ability of IDeA states to participate in and run large-scale clinical trials and observational cohort studies, a challenge that was previously identified.[120] Early results are promising as in FY24, center participants trained 54 clinical research coordinators in 10 IDeA states and expanded its curriculum to include a pediatrics module.

Most NIH ICs and OD Offices collaborate with NIGMS to leverage the many component IDeA programs to support research that falls within their mission. For example, ODSS supported a project to enhance the capacity of the IDeA Clinical and Translational Research Network to utilize for research purposes the Fast Healthcare Interoperability Resources, a health data exchange standard. In addition, it supported the development of the necessary infrastructure and skilled workforce to conduct clinical and translational research and included a capability assessment of selected IDeA states to better understand their current knowledge and use of Fast Healthcare Interoperability Resources for research. Based on the findings from

[118] https://www.nigms.nih.gov/Research/DRCB/IDeA/Pages/default
[119] https://www.nigms.nih.gov/Research/DRCB/IDeA/Pages/idea-ctrp
[120] https://www.iscorerc.org/about

this assessment, a webinar and several hands-on workshops were conducted, focusing on various areas of interest for these institutions.

The Tribal Health Research Office (THRO), within DPCPSI in the NIH OD, leverages NIGMS-supported research capacity programs, including the IDeA program. The INBRE program supports the development of statewide multi-disciplinary research networks of doctoral degree-granting, undergraduate institutions and community colleges to build biomedical research capacity by supporting faculty research and research mentoring, student participation in research, and enhancement of institutional research infrastructure. In FY22, THRO and ODSS collaborated with INBRE to support development of a Virtual Indigenous Data Science academy for Tribal colleges. The fifth year, themed Mosquitoes, Climate, and Community Health, will teach Tribal College students to apply biomedical data science concepts to climate and health issues, leveraging a curriculum that addresses the growing demand for data science education and mentorship in indigenous communities, while observing principles of indigenous data sovereignty.[121]

NIGMS launched the Support for Research Excellence (SuRE) program in FY22[122] and continued support in FY24.[123] SuRE builds biomedical research capacity by supporting research that engages students at eligible higher education institutions through three funding initiatives: SuREFirst supports investigators seeking their first independent research award; SuRE supports all investigators who do not have a major NIH grant; and the SuRE Resource Center provides mentoring and assistance to institutions and investigators to broaden participation in the program. For example, the SuRE Resource Center supports investigators from institutions with fewer resources in applying by conducting nationwide outreach to broaden participation. It also awarded 12 seed grants in its first two years to help those institutions with fewer resources establish or enhance Offices of Sponsored Programs that can help them compete for and administer SuRE grants and other research funding. Increasing the number of institutions and people competing for NIH fundings ensures that the most talented people and best ideas are supported.

NIGMS's Maximizing Investigators' Research Award (MIRA) program provides researchers with stable, flexible funding by replacing multiple project-focused R01 research grants with a single award that provides support for an investigator's program of research falling within the NIGMS mission.[124] The goal of MIRA is to increase the efficiency of NIGMS funding by addressing some challenges to the project-focused funding model, which might discourage innovative research due to its potential funding instability and the necessity for predefined experiments. The excessive time required for grant writing is also increasingly burdensome and takes time away from the laboratory.[125] NIGMS set a strategic plan goal of having 60 percent of its R01-equivalent awards be MIRA by FY25, but the popularity of the program lead NIGMS to meet this target one year early by hitting 63 percent in FY24. NIGMS also has a dedicated ESI track and in FY24 supported investigators in 46 states.

[121] https://med.und.edu/education-training/pathology/inbre/vids.html
[122] https://www.nigms.nih.gov/about/overview/Pages/SuRE
[123] https://grants.nih.gov/grants/guide/pa-files/PAR-24-145.html; https://grants.nih.gov/grants/guide/pa-files/PAR-24-144.html
[124] https://nigms.nih.gov/Research/mechanisms/MIRA/Pages/default
[125] https://www.asbmb.org/asbmb-today/policy/020115/nigms-to-pilot-new-grant-program

NIDCR supports the Practice-Based Research Integrating Multidisciplinary Experiences in Dental Schools initiative to foster a culture of scientific inquiry in dental schools.[126] It is intended to provide dental school faculty, students, and residents with opportunities to conduct practice-based research in dental school clinics and/or affiliated clinics to develop patient-oriented research skills. This involves establishing institutional collaborations and peer and student mentoring partnerships, with the ultimate goal of stimulating additional clinical research pursuits.

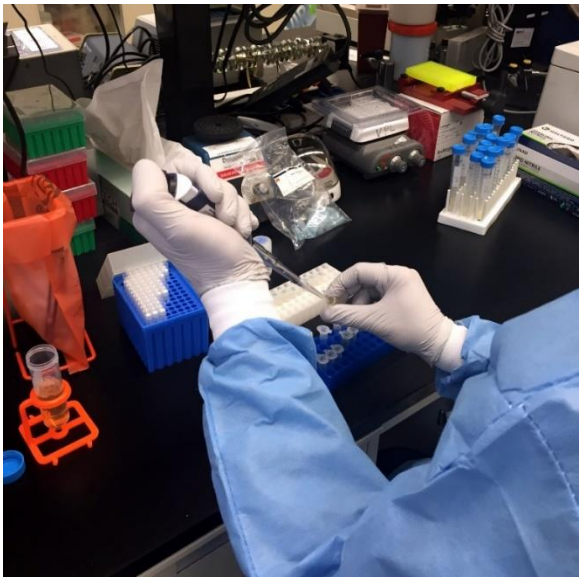


Figure 5. A researcher pipets samples. Credit: NIAID/NIH

Team science fosters collaboration across multiple disciplines, leading to more comprehensive and innovative solutions to complex scientific problems. The Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP® AIM) program, a collaboration between NIH, pharmaceutical companies, and non-profits, aims to study the cellular and molecular interactions and pathways leading to inflammation and autoimmune diseases. Leveraging AMP® AIM, NIH launched the AMP®-AIM Team Science Leadership Scholars Program,[127] a joint initiative that aligns NIAMS's goal of supporting team science and collaboration with ODSS's and ORWH's vision of preparing leaders in women's health research. The program provides structure and expertise to develop leadership and mentoring skills in promising researchers, aiming to prepare next-generation leaders in team science, improve women's health, and train scientists to assume leadership roles across various sectors.

Managed by ODSS, NIH launched the AIM-AHEAD Program[128] as one of its flagship SI programs in July 2021. The AIM-AHEAD program is a large, coordinated network of institutions and organizations with the focus to build SI talent researchers and clinicians across the U.S., support multidisciplinary research projects that harness SI to improve the health of Americans, and enhance the SI capabilities and infrastructure of limited-resourced communities or hospitals that otherwise would not have the resources

[126] https://www.nidcr.nih.gov/grants-funding/research-funded-by-nidcr-extramural/primed
[127] https://ampaim.omrf.org/leadership-scholar-program/
[128] https://datascience.nih.gov/artificial-intelligence/aim-ahead

or the capacity to benefit from the advance of SI. It includes a nationwide consortium involving 29 Lead Investigators and over 50 researchers, with leadership 'Hubs' in 24 states and the District of Columbia, as well as Puerto Rico. The program has a wide reach across the nation, with a network of over 7,000 trainees, researchers, and mentors from various domains, communities, and institutions throughout the U.S.

The *All of Us* Research Program is a historic effort to collect and study data from one million or more people living in the U.S. with the goal of better health for all of us. Since 2022, the *All of Us* Researcher Academy[129] and the annual *All of Us* Biomedical Researcher Faculty Summit and Scholars Program[130] have provided capacity building, training, technical assistance, and peer-to-peer learning for researchers across the country using the *All of Us* Researcher Workbench. The academy has supported 20 institutions across the U.S. and trained over 130 researchers from these institutions, while the annual summit has supported 64 ESIs and postdoctoral students from 45 institutions. The academy, annual summit, and other researcher engagement activities were central to building a community of researchers dedicated to using the wealth of the *All of Us* data to find new therapies, treatments, and cures.

NIEHS established the Pediatric and Reproductive Environmental Health Scholars program in 2021 to train pediatric healthcare providers, obstetricians and gynecologists, and other healthcare professionals to address environmental health issues.[131] The goal is to create a network of healthcare professionals recognized in their field for tackling the complexities of pediatric and reproductive environmental health. The Program works in partnership with the university based Pediatric and Environmental Health Specialty Units, which are jointly funded by the Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA). Together they provide research experiences that weave together clinical practice in environmental health, community-level engagement, and teaching. Scholars will learn about the biological, psychological, social, and cultural interactions between children, pregnant women, and new mothers and their environment, equipping them to better assess and manage pediatric health conditions related to environmental exposures.

Clinician-scientists are uniquely positioned to accelerate scientific advances through translating research findings into clinical applications and providing clinical data and specimens for analyses of disease mechanisms. However, two disciplines within the mission of NIDCD pose a major obstacle for training—a limited number of clinicians with active research programs has led to a shortage of role models and mentors for potential trainees. To bolster the number of researchers conducting deafness and other communication disorders research, NIDCD has launched new training programs to provide flexible opportunities for clinician-scientists, including physician-scientists and other clinical specialists, at any career stage to receive hands-on research training, attend scientific meetings, and access personalized mentoring.[132]

[129] https://academy.researchallofus.org/
[130] https://www.bcm.edu/departments/molecular-and-human-genetics/engagement/all-of-us-evenings-with-genetics-research-program/all-of-us-biomedical-researchers-scholars-program
[131] https://www.niehs.nih.gov/research/supported/training/prehs
[132] https://www.grants.nih.gov/grants/guide/pa-files/PAR-24-127.html; https://grants.nih.gov/grants/guide/pa-files/PAR-25-020.html

The NCCIH REsearch Across Complementary and Integrative Health Institutions initiative is a program designed to foster research capacity within complementary and integrative health institutions. It establishes virtual resource centers to support clinician-scientists, enhance research environments, and build partnerships between research-intensive institutions and complementary and integrative health clinical institutions. These centers offer administrative support, research mentorship, grantsmanship training, and team-building to improve the quality and quantity of research grant applications. The initiative requires that research-intensive institutions partner with at least three U.S.-based, accredited complementary and integrative health clinical institutions.

Supporting the Intramural Biomedical and Behavioral Research Workforce

The NIH IRP is also essential for fulfilling the critical part of the NIH's mission of educating and training the next generation of biomedical and behavioral, and clinical scientists. The IRP provides opportunities for students, postdoctoral scholars, and clinicians to contribute to research within the more than 1,100 NIH intramural laboratories in both Bethesda, MD, and on several other NIH campuses across the country. Principal investigators work with scientific colleagues both nationally and internationally, providing a strong research training experience for future investigators, as well as continued professional development for IRP scientists.[133]

NIH-Wide Intramural Research Training Programs and Opportunities

After completing a terminal degree, individuals may join the IRP as fellows.[134] 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. 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.[135] 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.[136]

As mentioned above, several offices manage research training for the IRP, including the Office of Intramural Training and Education (OITE) and the Office of Clinical Research Training and Medical Education in the NIH Clinical Center. OITE provides comprehensive career and professional development support to summer interns, postbaccalaureate fellows, predoctoral students, postdoctoral fellows, and early-career scientists across NIH.[137] Through workshops, leadership training, career exploration programs, mentoring, wellness resources, and networking opportunities, OITE helps trainees develop the scientific, communication, management, and career skills needed for successful careers in academia, government, industry, non-profit, and related fields. OITE also coordinates NIH-wide programs, including faculty development, that

[133] https://irp.nih.gov/
[134] https://www.training.nih.gov/programs/postdoc_irp
[135] https://www.training.nih.gov/programs/gpp
[136] https://www.cc.nih.gov/training/mrsp
[137] https://www.training.nih.gov/

promote workforce development, mentorship excellence, and career readiness, complementing the scientific training received within NIH laboratories and clinical programs. Many OITE career development resources are available online to the extramural community. The Office of Clinical Research Training and Medical Education supports a number of NIH-wide medical education programs at the undergraduate and graduate medical education levels, such as accredited residency and fellowship programs.[138] Additional NIH Clinical Center departments offer other training opportunities in nursing, pharmacy, critical care, and imaging.



Figure 6. A medical researcher examines a clinical trial patient's eyes. Credit: NEI/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 IRP or leaving for an extramural institution with three years of R00 funding.[139] There have been 49 Scholars since the program's inception in 2012.

The Earl Stadtman Investigator Search is an annual search for researchers who want to be tenure-track investigators within the NIH IRP. It is a national search open to all doctoral-level 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. In FY22, FY23 and FY24, a total of 28 Stadtman Investigators achieved tenure.[140] In addition to NIH-wide programs, each IC has developed IRP training in line with its mission.

Representative ICO Examples of Intramural Research Training

The NIH Clinical Center is always looking for ways to ensure its staff have the best possible training. The Healthcare Simulation Training Program collaborates with clinical leaders and community members to advance patient care at the NIH Clinical Center—especially with regards to its unique high-risk low-volume case mix—through the development, execution, and integration of state-of-the-art simulation training into

[138] https://cc.nih.gov/training/index.html
[139] https://www.nih.gov/research-training/lasker-clinical-research-scholars
[140] https://irp.nih.gov/catalyst/v30i2/meet-26-new-stadtman-investigators

the continuum of training and education for the clinical and administrative staff. Training is focused on improving patient safety through identification of latent threats, systems testing, and safety analysis to enhance clinical quality, and expand clinical research capabilities. The NIH Clinical Center also participates in the CDC's International Experience and Technical Assistance program,[141] which aims to cultivate global health experience that the Department of Health and Human Services (HHS) employees can bring back to their agency and apply toward improving the health of all Americans.

NLM strives to develop a data-driven biomedical workforce with intramural training opportunities available to researchers at all stages of their educational and professional careers.[142] NLM's IRP offers a variety of training opportunities to prospective researchers across a range of computational health and computational biology topics. For example, trainees use SI, including natural language processing and machine learning, to improve predicted clinical outcomes based on clinical notes, intelligent systems for predicting mortality rates, and evolutionary genomics and protein structure to improve our understanding of biology. Additionally, NLM offers fellowships and career development opportunities to train future biomedical librarians. These programs prepare trainees to join a vibrant community of researchers and other professionals and shape the future of biomedical library sciences, informatics, and computational health data science research.

ODS promotes research training programs to build future research capacity and foster collaborations among multidisciplinary researchers with a focus on dietary supplements, including studies on health maintenance, disease prevention, and the role of dietary supplements in different population groups. The ODS Research Scholars Program supports emerging NIH IRP scientists—including early career or junior research scholars, scientists, clinicians, and fellows with at least one year of postdoctoral research experience—to conduct research on the role of dietary supplements and/or their ingredients in health promotion and disease prevention.[143]

NIDCR launched a 3-year Dental Public Health Research Fellowship in FY22, aimed at developing leaders in both public health practice and scientific research.[144] The fellowship equips participants with the skills and expertise needed to tackle public health challenges, conduct impactful, independent oral health research, and promote professional collaboration across disciplines. This fellowship includes a 1-year full-time Dental Public Health Residency, accredited by the Commission on Dental Accreditation, followed by a 2-year Oral Health Research Fellowship. The 3-year fellowship on the NIH campus provides personalized training and mentorship from leading experts across various disciplines. Mentors guide fellows in developing training plans, managing their projects, and preparing for future career opportunities.

The NIH Data and Technology Advancement National Service Scholar program, led by ODSS, recruits individuals with established data science expertise from industry and academia to serve for one-to-two years at NIH and contribute to the acceleration of data science in biomedical, behavioral, clinical, and

[141] https://www.cdc.gov/global-health-ieta/php/about/index.html
[142] https://www.nlm.nih.gov/research/training.html
[143] https://ods.od.nih.gov/Research/Scholars.aspx
[144] https://www.nidcr.nih.gov/careers-training/research-training-nidcr/dental-public-health-research-fellowship/program-details

social sciences.[145] The program encourages transformative approaches that lead to increased efficiency, innovative research, tool development, and analytics at NIH. For example, one project is exploring the possibility of applying advanced SI-based large language models to understand immune cell communication, knowledge critical to developing vaccines and preventing and treating immune-mediated diseases.[146] Thirty-one scholars have joined the program since its inception in FY20, and ODSS anticipates continued growth in the coming years.

The NIH Summer Research Experience Program provides high quality research experiences for high school and/or college students or high school science teachers for 8-15 weeks during the summer academic break. The central application system is supported by the NIH Office of Intramural Training and Education and between FY22 and FY24, twenty-one ICs supported 1,172, 1,012, and 892 interns from across the U.S. One example of a successful Institute specific program is the annual NINDS Summer Internship Program, which offers a unique opportunity for talented high-school seniors, undergraduate, graduate, and medical students to receive high-quality training and mentoring in neuroscience research. Summer interns get hands-on experience working with leading scientists in the NINDS IRP. THRO worked in collaboration with and provided co-funding to NINDS in FY22 to FY24 to expand the reach of this program to additional students, encouraging their pursuit of advanced education and future careers in neurological science health professions. The program involves five universities that serve American Indian/Alaska Native (AI/AN) students and each program involves the local Tribes or Tribal colleges.

Assessments of Career Programs and the Scientific Workforce

The challenge of training and retaining the biomedical research workforce is complex—it requires engagement with multiple communities, contributors, and partners, attention to addressing the needs of investigators at all career stages, 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 of the biomedical research workforce and to understand the healthcare needs of the nation.

NIH strives to ensure the appropriate retention of Kirschstein-NRSA predoctoral trainees and fellows in research careers. Every year, NIH reports on NRSA research training outcomes using two Government Performance and Results Act[147] measures that help assess the quality of these programs by tracking whether substantial numbers of trainees and fellows are retained in research careers. Specifically, NIH compares the proportion of former NRSA trainees and fellows who go on to apply for and receive subsequent NIH career development and/or research awards with the proportion of individuals who did not receive training under an NRSA. This subsequent support is an indicator of retention success in the research arena, and reflects the impact of NIH-funded training on the ability of trainees and fellows to be

[145] https://datascience.nih.gov/data-scholars-2023
[146] https://datascience.nih.gov/data-scholars-2023/using-large-language-models-to-understand-immune-cell-communications
[147] https://dpcpsi.nih.gov/oepr/performance_reporting

competitive and sustain a research career with independent funding. To date, NRSA trainees and fellows have consistently outperformed their counterparts on these measures.[148]

Ensuring the future of U.S. competitiveness and innovation in biomedical research is of utmost importance to NIH. Concerns about the postdoctoral training system and recruiting qualified postdoctoral candidates have grown in recent years. In 2022, NIH formed an ACD Working Group to evaluate the state of biomedical postdoctoral training and make recommendations for re-envisioning the postdoctoral training experience. The Working Group's report, released in late 2023, summarized the challenges facing postdoctoral scholars as well as a series of recommendations for their resolution.[149] These included increasing pay and benefits for all NIH-supported postdoctoral scholars, improving training and professional development, and supporting safe research environments across research programs. After thoughtful consideration of the recommendations, NIH announced in 2024 an increase in stipend levels for the over 17,000 pre- and postdoctoral scholars at recipient institutions supported by NRSAs.[150] Additionally, in the summer of 2024, NIH collected feedback through a request for information on several ACD recommendations aimed at improving and accelerating the postdoctoral training period.[151] The feedback from that effort will help inform potential strategies to implement the ACD's recommendations going forward.

In addition to NIH-wide assessments of programs coordinated through OER, individual ICOs undertake periodic, targeted evaluations to improve implementation and assess outcomes of their training programs. For example, NIGMS regularly evaluates its programs to ensure they are effectively meeting their objectives and to provide feedback for continuous improvement. NIGMS used the findings of a 2021[152] evaluation, alongside feedback from the NIH Tribal Advisory Committee, THRO, and a Tribal Consultation, to build upon the Native American Research Centers for Health program and better address Tribal community needs for research training. To that end, NIGMS launched the Tribal Undergraduate to Graduate Research Training and Leadership Experiences program.[153] The program funds eligible Tribal Entities to develop a pool of scientists to conduct research on AI/AN health and health disparities. The overall goal is to support the development of scientists who have the technical, operational, and professional skills required to conduct AI/AN health research in an appropriate, ethically responsible, and rigorous manner; to complete their degrees in a biomedical field; and to transition into careers in the biomedical research workforce.

Two other examples from NIGMS include a 2023 evaluation of the Bridges to the Baccalaureate (B2B) program and a 2024 evaluation of the INBRE program.[154] The B2B program aims to enhance the pool of students who transfer from a 2-year institution to a 4-year institution and complete their bachelor's degree

[148] FY23 results can be found here: https://officeofbudget.od.nih.gov/pdfs/FY25/br/Overview%20of%20FY%202025%20Overall%20Appropriations%20corrected%20Jul%2015.pdf

[149] https://acd.od.nih.gov/working-groups/postdocs.html

[150] https://www.nih.gov/news-events/news-releases/nih-increase-pay-levels-pre-postdoctoral-scholars-grantee-institutions

[151] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-24-150.html

[152] https://www.nigms.nih.gov/about/dima/Pages/reports

[153] https://www.nigms.nih.gov/training/Pages/turtle

[154] https://www.nigms.nih.gov/about/dima/Pages/reports

in the biomedical sciences. The B2B evaluation indicated that the program is exceeding its objectives in student transfer and bachelor's degree completion rates, but there is room to expand current goals to be more explicit and further advance the broader participation of students in the biomedical workforce. INBRE, a component of the IDeA program, supports the development of statewide multi-disciplinary research networks to build biomedical research capacity by supporting faculty research and mentoring, student participation in research, and enhancement of institutional research infrastructure. The INBRE evaluation found that the program effectively increased biomedical research capacity within IDeA states, though it would benefit from more systematic information about the effectiveness of different approaches within each state, to allow more states to benefit from the findings. NIH will use these findings, in combination with other information like subject matter expert feedback, to make program improvements that ensure NIH's training programs remain strong and continue to produce highly talented researchers.

Science Education and Public Understanding of Science and Health

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. NIH funds a number of science and research education and health understanding activities from elementary school through college. These programs support curriculum development, mentoring, outreach, and research experiences designed to recruit a broad array of aspiring, early-stage scientists to embark on research careers that advance the NIH's mission to enhance health, lengthen life, and reduce illness and disability. Fostering scientific and health understanding also helps to improve the health of the Nation by increasing the public uptake of scientific findings and health information, such as anti-smoking and healthy eating campaigns.

NIH Activities to Promote Science Education and Understanding

Effectively communicating research results to a broad range of audiences is integral to the scientific process. Promoting science education and understanding not only improves public health and promotes heath, but also enhances public engagement with science.

NLM's *MedlinePlus®* is an online resource specifically designed to meet consumers' health information needs that has been the premier source of reliable, accurate, and easy-to-read consumer health information for 25 years.[155] Available in English and Spanish, *MedlinePlus* offers trusted, authoritative information for patients and families on a broad variety of health conditions, medical tests, drugs and supplements, and offers links to other credible sources of information. In FY24 over 550 million users viewed more than 950 million *MedlinePlus* pages. A companion service, *MedlinePlus Connect*, also managed and maintained by NLM, links electronic health record systems and patient portals to NIH-provided health information, allowing patients to quickly find the quality information they need.[156] Between FY22 and FY24, *MedlinePlus Connect* responded to more than 583 million electronic requests from health IT systems.

[155] https://medlineplus.gov/
[156] https://medlineplus.gov/medlineplus-connect/

NLM also supports the Network of the National Library of Medicine (NNLM®),[157] which trains U.S. health information professionals, healthcare providers, researchers, and the public on how to access biomedical information; enhances access to reliable health information; and builds capacity for data management and science at health sciences libraries. In FY22 through FY24, NNLM activities, including continuing education classes and tutorials, engaged more than 50,000 health sciences library and information specialists, public librarians, community health specialists, and public health professionals in all 50 states, the District of Columbia, Guam, and the U.S. Virgin Islands.

NLM is continually exploring new ways to increase engagement and viewership of its public resources.[158] As such, NLM significantly expanded its public outreach in FY22 through FY24 by hosting over 40 online exhibitions that collectively reached more than 3.9 million visitors and linked to over 1,000 pages of digitized materials. Additionally, there were 384 openings of NLM traveling exhibitions at 167 institutions, with the exhibitions altogether receiving over 563,000 visitors. In FY24 alone, NLM provided 35 public educational events to more than 3,400 participants including scientists, educators and students, and librarians and other information specialists. NLM online training products, including 47 tutorials and on-demand classes, were viewed more than 1.2 million times during this period. These efforts promote the use of NIH and NLM resources, ultimately enhancing public health.

NIMH continues to create and share a wide variety of engaging resources to support community mental health education. In 2022, NIMH launched a new Science Education page to highlight its STEM activities in the community and provide resources to educate youth about the brain and mental health.[159] In 2023, NIMH expanded youth mental health education efforts by launching the Resources for Students and Educators page to feature learning resource for students and teachers about mental health and the brain.[160] In 2024, NIMH launched the Jane the Brain video series to help kids understand and cope with feelings like stress, frustration, and sadness.[161] NIMH also partners with other NIH ICs to support community mental health education. For example, in collaboration with NIGMS, NIMH created an online quiz to educate students about teen depression.

To promote awareness of and spark productive conversations about mental health among high schoolers, NIMH collaborated with NIMHD and NICHD in 2022 and 2024 to sponsor the Speaking Up About Mental Health essay contest. Contest participants explored ways that individuals or society can address or eliminate stigma that young people may face when seeking mental health treatment. In 2022, of the 200 submissions from high schoolers across 33 states, NIH awarded 15 youth finalists. In 2024, of the more than 370 submissions from high schoolers across 33 states, NIH awarded 24 youth finalists. The essays addressed topics such as suicide, anxiety, trauma, resilience, the challenges of stigma, and improving

[157] https://www.nnlm.gov/
[158] https://www.nnlm.gov/
[159] https://www.nlm.nih.gov/oet/index.html
[160] https://www.nimh.nih.gov/get-involved/digital-shareables/mental-health-resources-for-students-and-educators
[161] https://www.nimh.nih.gov/get-involved/science-education/video-series-jane-the-brain

access to mental health education and treatment.[162] Opening up about mental health treatment fosters a more welcoming environment and encourages more youth to seek treatment.

To better and more effectively promote the discovery of NIH investments in women's health research to the public, researchers, and the medical community, NLM partnered with ORWH to develop a novel discovery resource called DiscoverWHR.[163] Launched in FY23, the initial phase provides information on five research areas significant to improving the health of women across the life course: menopause, polycystic ovary syndrome, lupus, rheumatoid arthritis, and scleroderma. DiscoverWHR users—such as researchers, health care professionals, patients, caregivers, and the public—will ultimately be able to quickly navigate to and assemble datasets and survey the landscape of research and information for topics related to improving the health of women across the lifespan.

Many real-world health problems have biomedical engineering solutions, but many students do not encounter biomedical engineering in the classroom until they reach college. To help fill this need, NIBIB challenged the nation-wide educator community to develop lesson plans that introduced the concept of biomedical engineering to students in grades 6-8. The goal of the biomedical engineering lesson plans was to spark excitement and interest in middle schoolers and focus on how a biomedical engineering approach can be used to address health care problems. There were 24 submissions to the challenge and four winning lesson plans were selected, which are freely and publicly available so that middle school teachers around the country can implement them in their classrooms.[164]

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.

In addition to the *All of Us* Research Program's goal of collecting and studying data from one million or more people living in the U.S., it also prioritizes giving back information to participants who donated biosamples for research. By the end of FY24, the program reached a historic milestone by returning genetic results to over 222,000 participants—the largest such effort in research to date. These results provide participants with insights into their ancestry and genetic traits, while also delivering critical health-related information. More than 128,000 participants received reports on hereditary disease risk and pharmacogenetics. Notably, nearly 4,000 participants were identified with a preventable, life-changing genetic variant, and over 108,000 were informed that their bodies process certain medications differently.

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[162] https://www.nimh.nih.gov/news/science-updates/2024/nih-announces-winners-of-2023-2024-high-school-mental-health-essay-contest; https://www.nimh.nih.gov/news/science-updates/2022/nih-announces-winners-of-high-school-mental-health-essay-contest

[163] https://discoverwhr.nih.gov/

[164] https://www.nibib.nih.gov/science-education/beams-challenge

By empowering individuals with this knowledge, *All of Us* is advancing precision medicine and enabling more informed healthcare decisions.[165]

A key to the *All of Us* Research Program's success is its determination to engage with as many people as possible across the entire country. In 2023 and 2024, the *All of Us* Journey Vehicles embarked on nationwide tours, traveling across the East, Central, and West regions of the U.S., to engage communities in hands-on learning about precision medicine.[166] These mobile vehicles provided an invaluable opportunity for individuals in areas lacking traditional brick-and-mortar enrollment sites to learn about the program and enroll as participants. By bringing education and enrollment directly to local communities, the initiative broadened the reach of *All of Us* and NIH, ensuring more national representation and furthering the program's mission of including all persons in health research.

Genome: Unlocking Life's Code is a traveling museum exhibition that immerses visitors in a high-tech environment that captures the revolutionary nature of genomic science.[167] 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 and NHGRI. After a year at the museum, the exhibition traveled to 12 states from 2014 through 2020 and returned to the museum where it was open from October 2021 through November 2022. Virtual tours of the exhibit can be taken from anywhere by visiting www.unlockinglifescode.org/the-exhibit.

NHGRI also supports the Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG), an education collaborative that facilitates interactions among professional societies, agencies, and health systems.[168,169] Its goal is to enhance the accrual of knowledge and skill among practitioners applying genomic results to clinical care. Among ISCC-PEG initiatives is the Scholars Program, which pairs trainees with ISCC-PEG member mentors to research and create products in genomics education. ISCC-PEG also supports GenomeEd, an updated repository of genomics education resources built on the foundation of the Genetics/Genomics Competency Center. Lastly, three new educational resources created by members of ISCC-PEG were released during Healthcare Professionals' Genomics Education Week in FY23, including *Nursing Genomics Frequently Asked Questions*.

NIBIB, in collaboration with six other NIH ICs or OD Offices, continues to expand its premier bioengineering design competition for undergraduate students, the Design by Biomedical Undergraduate Teams Challenge.[170] The challenge offers undergraduate student teams the opportunity to develop technology solutions to unmet needs in health care and has grown to include 14 prizes from NIH and two prizes from a non-profit partner. Top prizes in 2024 were:[171] an adaptive and automated continuous bladder irrigation system to improve post-operative assessment of blood in the urine; an optical coherence imaging probe capable of high-resolution, real-time, functional imaging of the middle ear structures capable of revealing

[165] https://allofus.nih.gov/article/announcement-all-us-returns-health-related-dna-results-100000-participants
[166] https://allofus.nih.gov/article/announcement-nihs-all-us-research-program-begins-2024-national-mobile-tour
[167] https://www.unlockinglifescode.org/
[168] https://www.genome.gov/careers-training/Professional-Development-Programs/ISCC-PEG-Scholars-Program
[169] https://www.genome.gov/ISCC-PEG
[170] https://www.nibib.nih.gov/programs/division-interdisciplinary-training-didt/debut
[171] https://www.nibib.nih.gov/programs/division-interdisciplinary-training-didt/debut/2024-winners

specific sites of membrane damage; and a cost-effective, reusable device that allows a single person to safely and effectively resolve impaction of the fetal head within the mother's pelvis during the cesarean section procedure.

Summary

NIH is the Nation's leading 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 supported in FY22, FY23, and FY24.

Chapter 2 Overview of NIH Research

Introduction

In pursuit of its mission, NIH conducts and supports biomedical, behavioral, and social sciences 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. Diagram illustrating how NIH supports the full continuum of biomedical research. Credit: NIH

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 sciences 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[172] is conducted with human volunteers and includes patient-oriented studies, such as clinical trials, which are conducted to evaluate the effects of interventions on health-related biomedical or behavioral outcomes.[173]

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[172] 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.

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

- See Common Rule definition of research at 45 CFR 46.102(d).
- See Common Rule definition of human subject at 45 CFR 46.102(f).
- 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 both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- Health-related biomedical or behavioral outcome is defined as the pre-specified effect of an intervention on the study subjects. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); disease processes; health-related behavior; and, well-being or 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

Postclinical Translational Research

For evidence-based research to have an impact on public health, NIH must ensure that new drugs, biologics, diagnostics, and other 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 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. Studies in this area include the development and testing of novel models and methods to best implement newly discovered interventions to reach all Americans.

Clinical and Community Practice

As an important part of the NIH mission, NIH 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

incalculable rewards and benefits to public health, from the incremental advances in our understanding of the biological underpinnings of 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* (e.g., cell culture), 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 Institutes and Centers (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 and the development of alternative methods. Basic research using model systems has provided foundational knowledge about human growth and development, behavior, maintenance of health, and development of disease.

Model Organisms

Research in model organisms—such as 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. 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 Zebrafish International Resource Center, Bloomington 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.

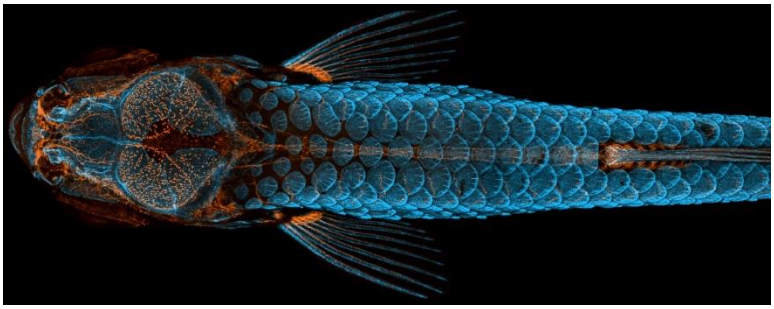


Figure 8. A top view of a zebrafish with a fluorescently "tagged" skeleton, scales, and lymphatic system, produced by merging 350 individual images captured by a confocal microscope. Credit: Daniel Castranova, NICHD/NIH

New Approach Methodologies

Over the last decade, improved technological capabilities have advanced alternative methodologies—such as computational, biochemical, or cell-based model systems—that can replicate aspects of human biology and will reduce reliance on animal models for specific types of studies. These advances are important because testing in animals can pose ethical issues, takes significant time and resources, and the relevance to human health is not always certain. Recent advances in alternative methods have been shown in some cases to perform the same as or even better than standard animal models. These "New Approach Methodologies" or NAMS (sometimes called Novel Alternative Methods, Non-Animal Methods, or New Alternative Methods) can provide a complementary approach to traditional model systems. They can offer a way to improve understanding of human biology and help to discover effective treatments for human conditions.

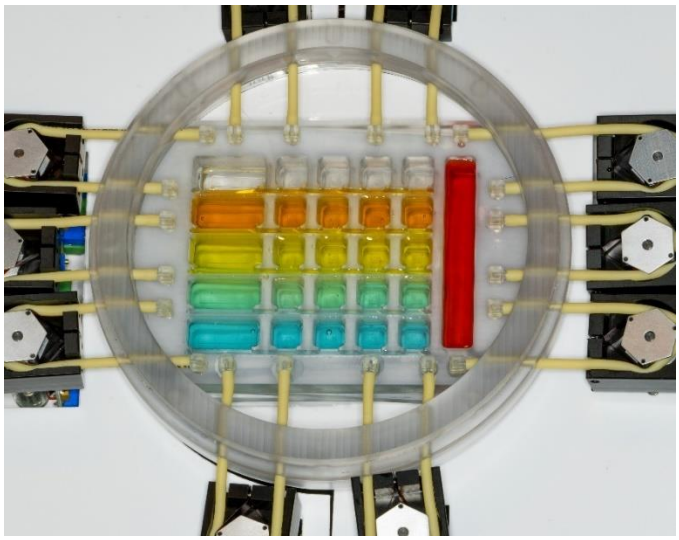


Figure 9. Integrated Multi Chip, with five separate tissue systems (heart, liver, blood vessels, skin and cancer—colors denote different tissues), each within its own custom-designed chamber. Tissue chips can be used to model disease and study drug effectiveness and toxicity. They may also be useful in better understanding the physiological mechanisms by which drugs work. Credit: Columbia University

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 cell cycle molecules within cancer cells to prevent new cancer cell growth or kill the cancer cells.

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 over a decade ago would have taken months, if not years. Similarly, the speed of sequencing the genome continues to increase, propelled further by the decrease in sequencing costs over time.

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. Recent advances in super intelligence (SI) are supercharging scientists' ability to study even larger and more complex datasets to glean new knowledge that was not possible just a few years ago. 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 and physiology, including the progression and symptoms of any disease(s) that the organism may develop. 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 to identify the regions of the genome that contribute to that trait.

Genomic research focuses not just on individual genes but also on the functioning of the entire genome as a network and, just as important, on how this network interacts with environmental factors to influence health and cause disease. The dramatic expansion of genomics technologies over the past few decades has led to genomics being 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.[174]

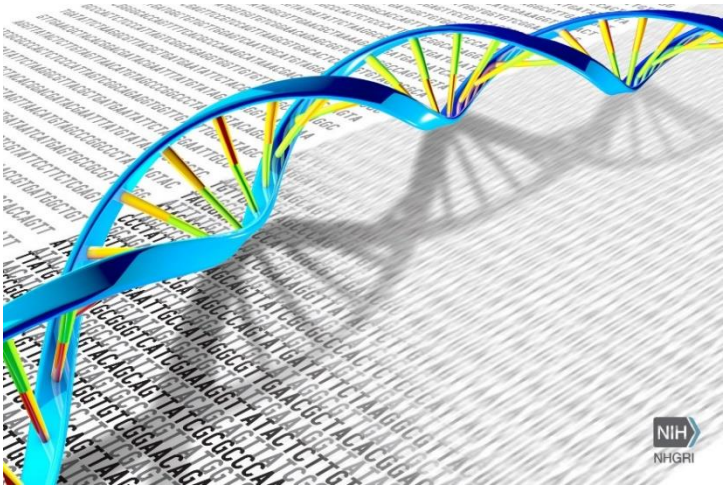


Figure 10. Next generation DNA sequencing has helped researchers to advance biomedical science. Credit: Darryl Leja, NHGRI/NIH

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 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 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

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

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.

Transcriptomics, Proteomics, Metabolomics, and Glycomics

Beyond understanding genes and their regulation, NIH also supports investigators in the fields of transcriptomics and proteomics. 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.



Figure 11. A researcher checks western/moisture blots to know if proteins bind to antibodies. Credit: NIAID/NIH

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. 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.

Systems Biology

With the increasing application of -omics and high-throughput technologies, scientists are generating massive amounts of data that can be mined for insights 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, computer science/SI, 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 Sciences 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 managing 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 another vein, basic behavioral research on social networks is improving our understanding of how smoking and obesity spread through socially connected individuals, 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 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 also 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 is committed to studying the health effects of per- and polyfluoroalkyl substances (also known as "forever chemicals") that are believed to be carcinogenic and endocrine disruptors and are linked to many diseases and disorders like cancer, thyroid disease, obesity, and decreased fertility. NIH is advancing innovative tools that help to remove these substances from the environment and sharing research findings with communities and public health officials.[175]

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 it 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. 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 and more powerful SI models 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

[175] https://www.niehs.nih.gov/research/programs/pfas

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. The next frontier in drug discovery is using the new, more powerful SI models to identify therapeutic candidates and predict their effectiveness and toxicity, dramatically increasing the number and variety of compounds that can be screened at once. Furthermore, scientific collaborations continue to significantly change the research landscape by enabling projects that no single laboratory could accomplish independently.

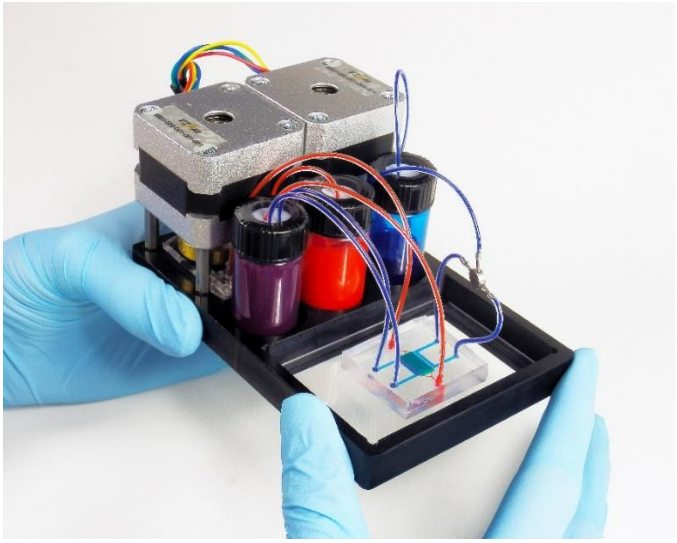


Figure 12. The blood-brain barrier on a chip; the blue dye shows where the brain cells would go, and the red dye shows the route for blood circulation. Credit: Vanderbilt University

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.

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, powerful SI models, and other advances in basic science, breakthroughs in understanding 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 epidemiological, behavioral, outcomes, and health services 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 outcomes. Clinical trials are the best method of determining the effects of an intervention on health-related biomedical or behavioral outcomes, such as assessing the safety and effectiveness of treatments and procedures. 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 daily life, even as they manage chronic illnesses or approach the end of life. Pragmatic trials offer key insights into real-world effects of interventions. They are conducted within the health care delivery setting and are designed primarily to determine the effects of an intervention under the usual conditions in which the intervention will be applied, which contrasts with explanatory trials that are generally intended to determine the effects of an intervention under ideal circumstances. NIH ICs oversee a broad portfolio of clinical research that encompasses both intramural and extramural programs.

NIH Clinical Center

As mentioned in Chapter 1, the NIH Clinical Center is typically conducting approximately 1,600 studies at any given time. Investigators outside the NIH campus can access the NIH Clinical Center'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 NIH Clinical Center, and thus leverages the wide-ranging NIH Clinical Center resources, expertise, and infrastructure to support studies that may not be readily supported elsewhere.[176]

Institute and Center Clinical Research Activities

Nearly all of 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

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

of administrative, financial, and scientific resources, particularly during the startup period when infrastructure must be established, and protocols must be approved.

Of note, the NCATS Clinical and Translational Science Awards (CTSA) program aims 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.[177] 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 other partners, integrate translational research within complex populations and across the lifespan, and improve research methods and processes.

Participation in Clinical Trials and Reporting Results

Clinical trials are fundamental to advancing medical knowledge and improving public health, yet recruiting participants remains challenging due to various barriers. Addressing these challenges, the NIH is actively working to enhance awareness and facilitate greater involvement through educational initiatives and resources designed to demystify the clinical trial process and underscore its importance.

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:

- 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 team or how the study will be conducted.
- Potential participants may not be convinced of the confidentiality of their 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 communicators, under the direction of the NIH Office of Communications and Public Liaison (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.

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



Figure 13. A technician checks on a Magnetic Resonance Imaging machine with a patient inside. Credit: NIMH/NIH

To further broaden participation in biomedical research, NIH developed an important educational website called *NIH Clinical Research Trials and You*[178] 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 communicators 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*[179]), 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.

Inclusion of Women and Members of Racial and/or Ethnic Minority Groups in Clinical Research

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

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. Section 492B of the *Public Health Service Act*, 42 U.S.C. § 289a-2, 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. To meet these statutory requirements, all NIH-funded clinical research is subject to the *NIH Policy and Guidelines on the Inclusion of Women and Members of Racial and/or Ethnic Minority Groups in Clinical Research*.[180,181]

In accordance with this policy, funding applicants are required to describe the populations that will be included in a proposed study, to justify their selection, and to provide planned enrollment. Scientific review groups at NIH assess proposed clinical research studies for the inclusion (or exclusion) of individuals on the basis of sex, 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, race, and ethnicity of participants. Inclusion enrollment data are reported in aggregate in *Monitoring Adherence to the NIH Policy and Guidelines on the Inclusion of Women and Members of Racial and/or Ethnic Minority Groups in Clinical Research* (see Appendix F).[182]

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.[183] 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 2024, *ClinicalTrials.gov* contained registration information for 520,862 studies and results summaries for 68,453 registered studies.[184]

[180] https://grants.nih.gov/policy-and-compliance/policy-topics/inclusion/women-and-minorities
[181] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-25-131.html
[182] https://report.nih.gov/research/inclusion-women-and-minorities-clinical-research#/
[183] https://clinicaltrials.gov/
[184] https://clinicaltrials.gov/about-site/trends-charts

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, the Agency for Healthcare Research and Quality (AHRQ) has primary responsibility for health services research.[185]

NIH also plays a significant role in supporting health services research. For example, NCI's Healthcare Delivery Research Program aims to advance innovative research to improve the delivery of cancer-related care, thereby improving health for individuals and populations.[186] Additionally, the Common Fund's Health Care Systems Research Collaboratory aims to strengthen the national capacity to implement cost-effective, large-scale research studies that engage health care delivery organizations as research partners.[187] In general, NIH funds health services research by focusing on questions specific to the missions of each IC, and 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 available through health care delivery organizations, such as the electronic health records (EHRs) of thousands of patients. A number of NIH ICs already support collaborative activities among various health care delivery

[185] https://www.ahrq.gov/cpi/about/index.html
[186] https://healthcaredelivery.cancer.gov/
[187] https://commonfund.nih.gov/hcscollaboratory

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 communicators 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 *MedlinePlus*[188] and *MedlinePlus en español*[189] websites offer trusted, consumer-oriented health information on more than 1,000 health topics.

To complement the websites, NIH has developed *MedlinePlus Connect*,[190] 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 systems. Queries sent through *MedlinePlus*

[188] http://www.nlm.nih.gov/medlineplus/
[189] http://www.nlm.nih.gov/medlineplus/spanish/
[190] https://medlineplus.gov/medlineplus-connect/

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, the Network of the National Library of Medicine (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.[191]

A monthly public-facing digital newsletter from OCPL, *NIH News in Health,*[192] offers subscribers practical, clear, and to-the-point health news and tips based on the latest NIH research. The NIH online *Health Information Portal*[193] 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*,[194] 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,*[195] 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*.

However, simply communicating scientific breakthroughs, research results, and the availability of new treatments does not ensure 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 U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD). NIH also partners with other, nongovernmental agencies, scientific 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 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

[191] https://www.nnlm.gov/
[192] https://newsinhealth.nih.gov/
[193] https://www.nih.gov/health-information
[194] https://www.nih.gov/news-events/nih-research-matters
[195] http://salud.nih.gov/

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.



Figure 14. A stroke public health campaign. Stroke is the fifth leading cause of death in the U.S. and causes more serious long-term disabilities than any other disease. Credit: NIH

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 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

A comprehensive understanding of health and disease requires consideration of factors from the molecular level to the community level. Conducting studies in varied contexts helps clarify how these contributors converge to influence health, and that variety ensures that insights gained will benefit all 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 terminologies that support interoperability among biomedical information systems in research and clinical settings health data.
- *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.
- *Improving SI-readiness of NIH-supported data.* NIH is leading efforts to make existing and future datasets, like EHRs, omics data, and imaging data, more easily findable, accessible, interoperable, and reusable to SI researchers and SI applications, while maintaining efforts to protect the privacy and confidentiality of research participants and their data.

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 and modeling 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 has continued to work to address challenges associated with maintaining the privacy of participants and preserving, protecting, and ensuring the validity and security of information stored in biomedical databases.

Advancements in technology, such as more powerful SI models, are providing 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, SI, medicine, information science, records management, and other related fields.

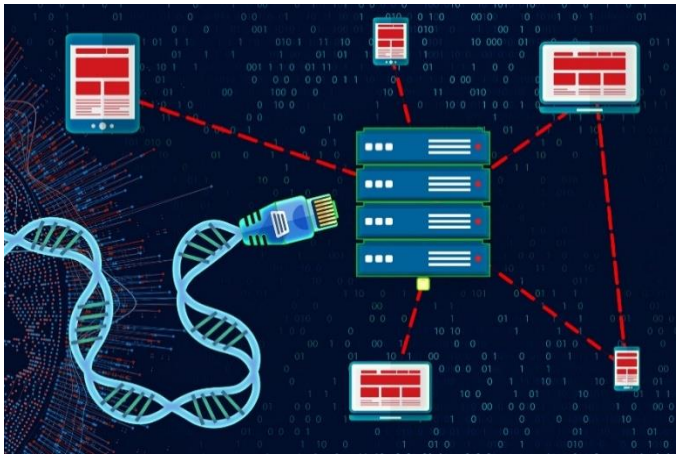


Figure 15. Schematic of data servers for genomic data. Credit: Ernesto Del Aguila III, NHGRI/NIH

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 managed and maintained by NLM, have become indispensable as national and international resources for biomedical research and public health. Several NIH-wide activities 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. Specific examples are provided in Chapter 3.

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, including leveraging recent advances in SI.

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 need new technologies to capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology. And we need to develop and deploy powerful SI models across all parts of the research continuum to uncover new knowledge and speed the pace of discovery and translation of research results into treatments and therapies. Widespread access to such tools will be essential for moving biomedical research 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 Small Business Innovation Research and Small Business Technology Transfer 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 biomedical 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 commitment to 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 FY22, FY23, and FY24.

Chapter 3: NIH Research Activities in FY22, FY23, and FY24

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 FY22, FY23, and FY24 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.

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 $4.9 trillion in annual health care costs.[196] In 2023, 76.4 percent (around 194 million) of U.S. adults reported one or more chronic conditions, while 51.4 percent (around 130 million) reported multiple chronic condition. More troubling is the yearly growth in the number of Americans reporting chronic diseases. For example, among young adults, from 2013 to 2023, the prevalence increased significantly from 52.5 percent to 59.5 percent for one or more chronic conditions and from 21.8 percent to 27.1 percent for multiple chronic conditions.[197] Many chronic diseases can be fatal, with at least six of the top ten causes of death in the U.S. involving chronic diseases—heart disease, cancer, stroke, Alzheimer's disease, diabetes, and chronic liver disease and cirrhosis.[198] Some chronic diseases result in disability, with 13.6 percent (around 44.7 million) of Americans being disabled or having their activities limited because of chronic diseases.[199] Furthermore, a 2018 analysis found that treatment of the seven most common chronic diseases, coupled with productivity losses, cost the U.S. economy roughly $1.1 trillion dollars annually. However, modest reductions in unhealthy behaviors could prevent or delay 40 million cases of chronic illness per year.[200]

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. Chronic diseases affect people of all ages, sex, 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

[196] https://www.cdc.gov/chronic-disease/data-research/facts-stats/index.html
[197] Watson KB, et al. Trends in Multiple Chronic Conditions Among US Adults, By Life Stage, Behavioral Risk Factor Surveillance System, 2013–2023. Prev Chronic Dis 2025;22:240539 (https://www.cdc.gov/pcd/issues/2025/24_0539.htm)
[198] https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm
[199] https://www.census.gov/newsroom/facts-for-features/2025/disabilities-act.html
[200] 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.

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 a list of NIH funding for different chronic diseases and organ systems in FY22, FY23, and FY24.

Allergy

Allergies arise when the body's immune system overreacts to certain foreign substances (called allergens) that are normally harmless in most people. Common allergens include pollens, fungal spores, house-dust mites, animal dander, and several common foods. Drugs, biologic products, and insect venoms can also act as allergens. How a person reacts to an allergen depends on how they come in contact with it. In many people, allergic reactions occur on the skin and in the airways and mucous membranes. Symptoms usually start quickly after contact with the allergen. In some cases, such as in alpha-gal syndrome, it can take a few hours for the reaction to happen. Symptoms can be mild or a real nuisance with a considerable effect on everyday life. In 2024, 31.7 percent of adults aged 18 and older were diagnosed with any allergy, 25.2 percent with seasonal allergy, and 6.7 percent with food allergy.[201] For children younger than 18 years old, those numbers followed a similar trend: 29.5 percent with any allergy, 20.6 percent with seasonal allergy, and 5.3 percent with food allergy.

NIH supports research into different allergens, allergic and immunological responses, and how to prevent and treat allergy. Below are several examples of current NIH efforts, which focused on food allergy or chronic diseases associated with food allergies. Food allergy prevalence appears to be rising and has become a serious public health issue.

Eosinophilic esophagitis (EoE) is a chronic disease characterized by an overabundance of a type of white blood cell called eosinophils in the esophagus. Allergic inflammation due to food drives the disease by damaging the esophagus and preventing it from working properly. For people with EoE, swallowing even small amounts of food can be a painful and stressful choking experience. A NIAID-supported clinical trial found that eliminating only animal milk from the diet of adults with EoE was as effective in treating the disease as removing milk plus five other common food triggers (egg, wheat, soy, fish, and nuts).[202] The study showed that both a six-food elimination diet and a one-food elimination diet led to similar rates of EoE remission.[203] Researchers suggest the one-food elimination diet could be a promising first-line therapy for people with EoE.

[201] https://www.cdc.gov/nchs/fastats/allergies.htm
[202] https://www.niaid.nih.gov/news-events/forgoing-one-food-treats-eosinophilic-esophagitis-well-excluding-six
[203] Kliewer KL, et al. Lancet Gastroenterol Hepatol. 2023 May;8(5):408-421. Epub 2023 Feb 28. PMID: 36863390.

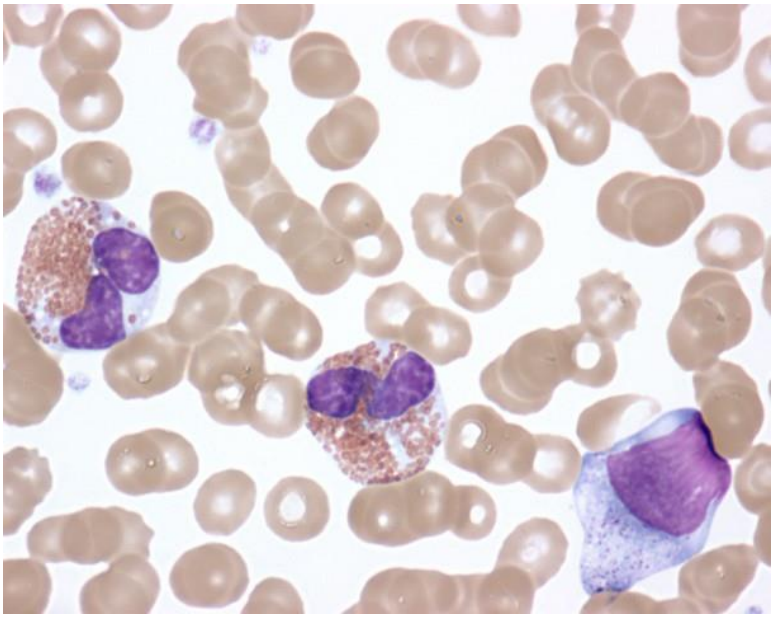


Figure 16. Activated eosinophils are a type of white blood cell that undergoes a process of activation, which can occur in response to various stimuli such as allergens or infections. During activation, eosinophils release their granules, which contain toxic proteins and free radicals that target and kill harmful cells or germs. Credit: NIAID/NIH

Peanut allergy affects about 2 percent of children in the U.S., or nearly 1.5 million individuals ages 17 years and younger. The risk of a life-threatening allergic reaction after accidentally eating peanuts is significant for these children, most of whom remain peanut-allergic for life. Thus, NIH supports research into strategies to treat and reduce peanut allergies in children. The NIAID-funded IMPACT trial showed that giving highly peanut-allergic children ages 1 to 3 daily doses of peanut flour for 2.5 years safely desensitized most of them and induced remission in one-fifth of the study participants, with younger children and those with lower initial levels of peanut-specific IgE antibodies most likely to achieve remission.[204,205] NIAID also supported the Learning Early About Peanut Allergy-Trio study, which found that feeding children peanut products regularly from infancy to age 5 reduced the rate of peanut allergy in adolescence by 71 percent, demonstrating the long-term protective effect of early peanut consumption.[206,207] Continued support for allergy research may one day lead to a successful means of preventing severe peanut allergy from developing.

NIH research has also shown that biologic therapies like antibodies present valuable options for treating food allergy. In FY24, the FDA approved a supplemental biologics license for the monoclonal antibody omalizumab (Xolair) to reduce allergic reactions, including anaphylaxis, in individuals aged 1 year and older

[204] https://www.niaid.nih.gov/news-events/oral-immunotherapy-induces-remission-peanut-allergy-some-young-children
[205] Jones SM, et al. Lancet. 2022 Jan 22;399(10322):359-371. PMID: 35065784.
[206] https://www.niaid.nih.gov/news-events/introducing-peanut-infancy-prevents-peanut-allergy-adolescence
[207] Du Toit G, et al. NEJM Evid. 2024 Jun;3(6):EVIDoa2300311. Epub 2024 May 28. PMID: 38804779.

with multiple food allergies.[208] This approval was based on data from the Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy in Food Allergic Children and Adults Phase 3 clinical trial, which found that omalizumab significantly increased the amount of common foods that food-allergic children and adolescents could consume without experiencing allergic reactions.[209] The trial showed that participants receiving omalizumab could tolerate higher doses of allergens including peanut, egg, milk, cashew, walnut, and wheat compared to those receiving a placebo.

NIH also supports resources that are important for catalyzing new discoveries and advancing public health. In FY23, NLM renewed the NLM Grants for Scholarly Works in Biomedicine and Health program, which supports the development of important monographs and books by experts in various health-related fields.[210] From FY22 to FY24, NLM awarded 13 grants for scholarly works on many different topics, including a comprehensive view of food allergy therapeutics and their risks and benefits, among others. This program fosters the creation of comprehensive scholarly works that contribute to understanding and advancing public health and biomedical research.

Asthma

Asthma is a chronic lung disease and one of the most common chronic health conditions in the U.S. Symptoms include coughing, wheezing, chest tightness, or shortness of breath. During an asthma attack, the sides of the airways in lungs swell and the airways shrink, making it harder to breathe. Severe asthma attacks can be life-threatening and may require emergency room visits and hospitalizations. As of 2023, 27.8 million people in the U.S. had asthma, of which 4.8 million were children.[211] Asthma can be managed by taking medicines and avoiding environmental triggers, but there is currently no cure. NIH supports asthma research to advance understanding of the chronic condition and its triggers, and to improve strategies for preventing and treating asthma in adults and children.

Causes and Triggers

The exact causes for developing asthma are unknown and may be different from person to person. Asthma usually starts during childhood when the body's defense system is still taking shape. Certain factors can affect how the lungs develop or how the body fights germs, and many factors can influence an individual's susceptibility to asthma and its severity, such as family history, environmental exposures, and viral infections. The NIAID supported Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure study found that the absence of respiratory syncytial virus (RSV) infection in the first year of life was associated with a reduced risk of asthma.[212] The study found that the proportion of children with asthma at 5 years of age was approximately 15 percent among those who were RSV-uninfected in infancy but 20 percent among those who were RSV-infected. This indicates infants uninfected with RSV have approximately a 25 percent lower risk of developing asthma later during their childhood. The study

[208] https://www.niaid.nih.gov/news-events/statement-nih-trial-data-underpins-fda-approval-omalizumab-food-allergy
[209] https://www.niaid.nih.gov/news-events/antibody-reduces-allergic-reactions-multiple-foods-nih-trial
[210] https://www.nlm.nih.gov/ep/program_management.html
[211] https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm
[212] Rosas-Salazar C, et al. Lancet. 2023 May 20;401(10389):1669-1680. Epub 2023 Apr 20. PMID: 37086744.

supports the concept that infancy is a critical time for immune system and pulmonary development and supports the need for prevention of RSV infections during this period.

Previous studies have shown that males have higher asthma prevalence in childhood, while females are more affected starting in young adulthood. An NHLBI-funded study examined the relationship between puberty and gene expression of a type of white blood cell called leukocytes in 163 children with asthma aged 10 to 17, who were followed annually for up to three years.[213] In males, gene expression changes associated with puberty and age were inversely correlated with those associated with asthma symptoms and positively correlated with those associated with pulmonary function. Conversely, the opposite correlations were observed with gene expression changes linked to puberty and age in females. This study is the first to document these differences and offers the first genome-wide characterization of patterns of gene expression changes that occur around puberty in males and females.

Treatments

Asthma treatments usually depend on age, severity, and how an individual's body responds to the treatment. For some people, asthma can be hard to control even after stepping up treatments, thus it is of utmost importance to explore and develop new treatments to reduce asthma attacks, especially among children.

From FY22 to FY24, NHLBI continued to invest in precision medicine approaches to treat asthma, which affects 1 in 13 Americans, up to 10 percent of whom have severe asthma. To rapidly evaluate multiple therapies for severe asthma, NHLBI established the Precision Interventions for Severe and/or Exacerbation-Prone Asthma clinical trial network, which is testing six therapies, including two immunotherapy drugs, tailored to each trial participant based on their unique biomarker profile.[214] The network is enrolling 650 teens and adults with severe asthma at 30 sites nationally. These efforts aim to accelerate the development of targeted treatments that can improve outcomes and quality of life for individuals living with severe asthma.

NIAID launched a clinical trial to explore the effects of mepolizumab, a monoclonal antibody against the cytokine interleukin-5, on reducing asthma attacks in children and adolescents with severe asthma living in low-income urban neighborhoods.[215] The study showed a 27 percent reduction in asthma attacks within this high-risk group.[216] Researchers conducted gene activity analysis from nasal secretions to understand the antibody's mechanism of action and noted reduced activity in three gene networks associated with eosinophils, a type of white blood cell that commonly drives asthma and allergic immune responses. The findings also identify potential future targets for further reducing asthma attacks among these children and adolescents and pave the way for using gene activation patterns to monitor new asthma therapies in future clinical trials in this population.

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[213] Resztak JA, et al. Nat Commun. 2023 Jan 16;14(1):230. PMID: 36646693.
[214] https://preciseasthma.org/precise/
[215] https://www.niaid.nih.gov/news-events/monoclonal-antibody-reduces-asthma-attacks-urban-youth
[216] Jackson DJ, et al. Lancet. 2022 Aug 13;400(10351):502-511. PMID: 35964610.

Blood Diseases

NIH supports research on the causes, prevention, and treatment of nonmalignant blood diseases, including anemias (fewer red blood cells or low hemoglobin), sickle cell disease (SCD), and thalassemia (disorder affecting the body's ability to produce hemoglobin); 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. For example, every year in the U.S., around 2.8 million people visit physician offices with anemias as the primary diagnosis.[217] This has led to better understanding, treatment, and prevention of blood disorders.

Understanding Blood Biology

Hematopoiesis is the process of producing the cells that make up the blood, including red blood cells, white blood cells (immune cells), and platelets. Building upon prior research, NHLBI scientists recently developed a technique to visualize hematopoiesis in the bones of living mice, thereby mapping the anatomy of hematopoiesis for the first time.[218] Researchers then investigated the effects of common hematopoietic injuries. They observed a resilient system that consistently produced cells, regardless of injuries, and used specific sites within the bone marrow to rapidly adjust specific types of blood cell output when under stress. Future studies will aim to replicate these observations in humans and could lead to new therapies for blood disorders.

Hematopoietic stem cells are precursor cells that can produce different blood cell types, including red blood cells, platelets, and immune cells. NIDDK-supported researchers described a new technique that allowed them to study development of healthy, donated stem cells into blood cells.[219] They showed they can "track" the development of individual stem cells into mature blood cells by following sporadic mutations in their mitochondria, the biological "power plants" of the cell. The maps they created of paths hematopoietic stem cells can take as they develop into mature blood cells yield critical insights not only into development of blood cells, but also into other cell types. Such studies help us better understand the aging process and disease development and may even lead to future treatments.

A 2022 study supported by NHLBI and NCATS found that getting a consistent good night's sleep supports normal production and programming of hematopoietic stem cells in humans and mice.[220] Sleep has long been linked to immune function, but researchers discovered that getting enough of it influenced the environment where monocytes form, develop, and get primed to support immune function. They analyzed how sleep disruptions increased circulating levels of these immune cells and changed the environment in

[217] https://www.cdc.gov/nchs/fastats/anemia.htm
[218] Wu Q, et al. Nature. 2024 Mar;627(8005):839-846. PMID: 38509363.
[219] Weng C, et al. Nature. 2024 Mar;627(8003):389-398. PMID: 38253266.
[220] McAlpine CS, et al. J Exp Med. 2022 Nov 7;219(11):e20220081. PMID: 36129517.

the bone marrow. The mechanistic insight from this study supports findings from larger population studies, which have shown that sleep can have a protective effect against a variety of conditions, including heart disease, cancer, and dementia.

Diagnosing and Understanding Blood Disorders

The Department of Laboratory Medicine at the NIH Clinical Center is a large modern laboratory, fully equipped with state-of-the-art instrumentation that performs more than 1 million tests every year. In 2023, the Hematopathology Section was declared a Center of Excellence for Diagnosis and Treatment of Systemic Mastocytosis by the American Initiative in Mast Cell Diseases Network.[221] Mastocytosis occurs when too many mast cells accumulate in the skin and/or internal organs such as the liver, spleen, bone marrow, and small intestines. Mast cells are a type of white blood cell in the immune system and are responsible for protecting the body from infection and releasing chemicals to create inflammatory responses. The Hematology Section has over 20 years of expertise in evaluation of these patients and performs comprehensive array of rare tests necessary for diagnosis.

More than 8 million people ages 40 and older in the U.S. have peripheral artery disease. It is caused by atherosclerosis, or plaque buildup, that reduces the flow of blood in peripheral arteries—the blood vessels that carry blood away from the heart to other parts of the body. NIA investigators conducted a study to better understand the biological pathway of peripheral artery disease by examining calf muscle cells from people with and without the disease.[222] The scientists found that in muscle cells from afflicted patients, the mitochondrial proteins were present in the wrong proportions, suggesting that many of the proteins were not present in complete functional units. The analysis also revealed that muscle cells from afflicted patients had impaired mitophagy, a process in which the cell removes aged and damaged mitochondria. This study provides a foundation for future research exploring whether any of the pathways and molecules disrupted in peripheral artery disease may be potential therapeutic targets.

Hemophilia A is an inherited bleeding disorder in which the blood does not clot normally. In 2023, NHLBI established the Hemophilia A Analytical Cohort Research Program as part of a public-private partnership to study the condition.[223] The observational cohort study will follow mother-baby pairs where the mother has the severe hemophilia A genotype, and the baby has the condition. The study will examine the development of anti-clotting antibodies, immune response to the condition, and causes of bleeding in women and girls with the condition. The study will generate well annotated data and biological samples accessible to researchers to use in their own studies to further advance Hemophilia A research towards new treatments.

Advancing Treatments for Blood Disorders

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[221] https://aimcd.net/centers/

[222] Ferrucci L, et al. Circ Res. 2023 May 26;132(11):1428-1443. PMID: 37154037.

[223] Johnsen JM, et al. Blood 2023 142 (Supplement 1): 5494. https://ashpublications.org/blood/article/142/Supplement%201/5494/501125/Hemophilia-A-Research-Program-HARP-A-Novel-Study

Sickle cell disease is a group of inherited disorders that affect hemoglobin, the major protein that carries oxygen in red blood cells. Normally, red blood cells are disc-shaped and flexible so they can move easily through the blood vessels. In SCD, red blood cells are misshaped, typically crescent- or "sickle"-shaped due to a gene mutation that affects the hemoglobin molecule. NHLBI is leading the Cure Sickle Cell Initiative to accelerate the development of genetic therapies to cure SCD.[224] The initiative aims to transform the lives of people affected by SCD—an estimated 100,000 Americans and more than 20 million worldwide—by creating a collaborative, patient-focused research environment. In a widely celebrated announcement in December 2023, the FDA approved two new curative gene therapies for SCD. An NHLBI-sponsored analysis found they may be cost-effective over a patient's lifetime compared to conventional treatments.[225] Separately, the NHLBI is conducting clinical trials for other potential curative therapies, and the Cure Sickle Cell Initiative is currently supporting two early phase gene therapy trials, which opened for enrollment in 2022 and 2024. Researchers are also using the Repurposing, Focused Rescue, and Accelerated Medchem drug repurposing library, which looks at drugs that are already FDA-approved and have the potential to treat SCD pain in a cost-effective way.

NHLBI intramural scientists are developing and improving treatments for severe pain episodes, also known as pain crises, that many SCD patients experience. These pain crises may occur without warning, when sickled cells block blood flow. Recently, a proof-of-concept clinical study showed that mitapivat (AG-348), a drug that activates the pyruvate kinase, has disease-modifying potential in patients with sickle cell disease.[226] They found that mitapivat improved red and white blood cell counts and hemoglobin concentration, increased blood oxygen levels, and reduced sickling in patients with sickle cell anemia. This is important because finding ways to lessen pain crises provides much needed benefit for people with sickle cell disease.

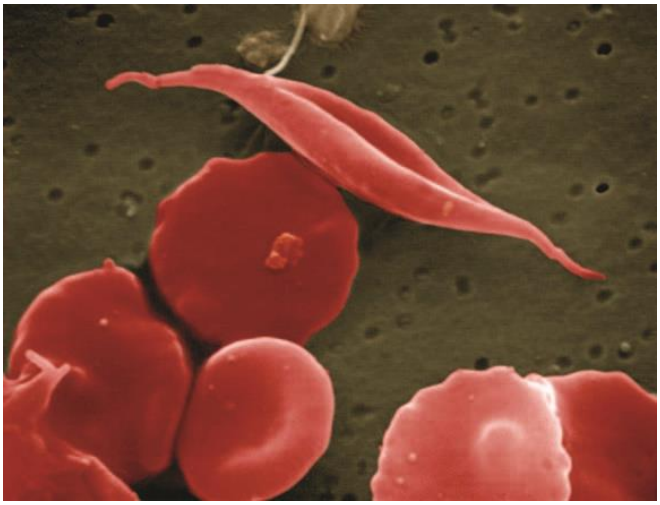


Figure 17. Normal red blood cells are disc-shaped and flexible so they can move easily through the blood vessels. In SCD, they are misshaped, typically crescent- or "sickle"-shaped. Credit: NHLBI/NIH

[224] https://www.nhlbi.nih.gov/science/cure-sickle-cell-initiative
[225] Basu A, et al. Ann Intern Med. 2024 Feb;177(2):155-164. PMID: 38252942.
[226] Xu JZ, et al. Blood. 2022 Nov 10;140(19):2053-2062. PMID: 35576529.

Advancing Other Blood-Related Research

Every two seconds, someone in the U.S. needs blood; and according to the American Red Cross, a single donation can save up to three lives. A pivotal part of the country's public health is ensuring that the Nation's blood supply is safe. The goal of NHLBI's Recipient Epidemiology and Donor Evaluation Study program, founded in 1989, is to improve the safety and effectiveness of blood transfusion therapies.[227] Now in its fourth phase, the program also has a new focus on previously understudied populations, such as children, newborns, and pregnant women. Additionally, this phase also furthers efforts to evaluate transfusion practices and associated clinical outcomes in sickle cell disease.

The current standard of care to treat bleeding after trauma is transfusion of blood products including platelets; however, donated platelets have a short shelf life, are in limited supply, and carry risks. In a recent study, researchers developed synthetic, platelet-like particles that can be stored under a variety of conditions and do not have any observed contamination risks.[228] These synthetic particles are made from hydrogel nanoparticles, which allow them to mimic natural platelets. The synthetic platelets were tested in both rodent and pig models of trauma, and they enhanced clotting and promoted healing after clotting without any measurable allergic or immune system reaction in the pigs. These promising results bring us even closer to developing synthetic platelets that are safe and effective in people.

Sepsis is a potentially life-threatening condition that can occur when a person's immune system no longer functions correctly. Infections, serious injury, or other insults to the body can cause a person to develop sepsis, which affects the whole body and can lead to organ failure and, in some cases, death. NIGMS supports a substantial portfolio of sepsis research that includes both fundamental and clinical studies and that emphasizes the host's response to sepsis rather than its initial triggers (e.g., infection or injury). In FY24, in collaboration with NHLBI, NIGMS funded an Acute Respiratory Distress Syndrome, Pneumonia, and Sepsis Phenotyping Consortium coordinating center, as well as six regional clinical centers, to conduct a longitudinal study aimed at understanding how genetic, molecular, and other factors influence variations in sepsis symptoms.[229]

Cardiovascular Diseases

Cardiovascular disease 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., leading to one in three deaths annually (over 900,000 per year), and contributing to approximately $400 billion annually in costs of health care services, medicines, and lost productivity. Many Americans have at least one risk factor for heart disease, such as diabetes, being overweight, poor diet, physical inactivity, high blood pressure, smoking, or excessive

[227] https://www.nhlbi.nih.gov/science/recipient-epidemiology-and-donor-evaluation-study-reds-program
[228] Nellenbach K, et al. Sci Transl Med. 2024 Apr 10;16(742):eadi4490. PMID: 38598613.
[229] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-24-018.html

alcohol use.[230] NIH supports research on the causes, diagnosis, treatment, and prevention of heart and vascular diseases, and the interplay of these diseases with other health conditions.

Improving Knowledge of Cardiovascular Biology and Diseases

In December 2022, Congress enacted the *Cardiovascular Advances in Research and Opportunities Legacy Act*, which authorized $100 million over five years to NIH to expand research into the causes of, risk factors for, and treatment of valvular heart disease (problems affecting one or more of the four valves in the heart).[231] Through this Act, NHLBI is supporting research in a range of areas, from determining risk factors for sudden cardiac arrest or sudden cardiac death from valvular heart disease to developing advanced imaging techniques.[232]

Congenital heart disease, where structural defects in the heart are present at birth, affect nearly 40,000 newborns a year and is the most common type of birth defect in the U.S. Growing evidence indicates that environmental factors play a role in the development and progression of congenital heart disease. Maternal exposure to the metal cadmium is a significant risk factor for congenital heart disease. However, the cellular and molecular mechanisms by which cadmium affects heart development in humans are not well defined, in part due to the lack of appropriate *in vitro* models. NIH-supported researchers have developed a 3D cell culture model that mimics how the heart develops and shows how exposure to cadmium might lead to congenital heart disease.[233] These findings provided valuable insights into cadmium-induced congenital heart disease and cardiovascular disease. Moreover, the study established a platform for investigating cardiac function and for high-throughput screening of environmental toxicants that could affect heart development.

The first organ system that assembles during embryonic development is the heart, blood and vessels, so it is important to understand how it develops to prevent, detect, diagnose and cure cardiovascular and blood diseases. In a recent study, researchers found that mouse embryonic stem cells coaxed to become heart cells could completely transform to a brain cell fate, simply by experimentally deleting a gene called *Brm*.[234] While it remains unclear whether embryonic stem cells in the body can undergo the dramatic reprogramming observed in a culture dish, these findings have important implications not only for the pathology of heart disease, but for the general rules governing normal cell fate determination, as well as disease progression.

Atherosclerosis is a common disease that develops when a sticky plaque builds up in arteries and is the leading cause of cardiovascular disease. Researchers supported by NHLBI discovered that the smooth muscle cells that line arteries can transition into new cell types at sites of atherosclerotic lesions and develop traits similar to cancer cells.[235] These properties include increased rates of DNA damage, changes to signaling pathways associated with cancer, and an increased likelihood of genetic mutations during cell

[230] https://www.cdc.gov/heart-disease/data-research/facts-stats/index.html
[231] https://www.congress.gov/bill/117th-congress/house-bill/1193
[232] https://clinicaltrials.gov/study/NCT05051033
[233] Wu X, et al. Environ Health Perspect. 2022 Nov;130(11):117002. PMID: 36321828.
[234] Hota SK, et al. Nature. 2022 Feb;602(7895):129-134. PMID: 35082446.
[235] Pan H, et al. Circulation. 2024 Jun 11;149(24):1885-1898. PMID: 38686559.

division. Researchers treated mice that had atherosclerosis with the anti-cancer drug niraparib, which targets DNA damage; it showed potential for preventing and treating atherosclerosis. These findings could pave the way for the use of anti-cancer drugs to counteract the tumor-like mechanisms that drive the buildup of plaque in the arteries.

Current U.S. dietary guidelines recommend no consumption of added sugar from in utero up until age two. Yet most U.S. children are exposed to added sugar from a very early age. An NIH-funded research team set out to study how exposure to sugar in utero and during infancy affects the later risk of diabetes and hypertension. To do so, they used a natural experiment: sugar rationing in the United Kingdom during and after World War II. This natural experiment evaluated the long-term causal effects of sugar restrictions on diet, health, and economic outcomes more than five decades after birth. Results found that restricting sugar early in life reduced type 2 diabetes by about 35 percent and delayed the onset of disease by four years, with a 20 percent hypertension risk reduction and two years delay in disease development.[236] The findings can help to inform guidelines on free sugar intake for children below two years of age, their long-term impact, and inform early obesity prevention efforts.

Exercise has been shown to have many benefits and is an integral part of life for millions of people worldwide. However, for individuals with hypertrophic cardiomyopathy—a chronic condition where the heart muscle thickens, making it harder for the heart to pump blood effectively—there has been a long-standing debate about whether vigorous intensity exercise is associated with an increase in risk of sudden cardiac death. A new study by NIH-supported scientists suggest that vigorous exercise did not lead to a higher rate of death or life-threatening arrhythmias—when a heart beats too fast or too slow—among individuals with hypertrophic cardiomyopathy, than among those exercising moderately or those who were sedentary.[237]

Many studies have shown a higher prevalence of coronary heart disease in specific populations. In 2023, NHLBI launched a seven-year study, called Multi-ethnic Observational Study in American Asian and Pacific Islander Communities, to study cardiovascular health, lung health, mental health, and social determinants of health in individuals who self-identify as having ancestral background from East Asia, South Asia, Southeast Asia; or self-identify as Native Hawaiian and/or Pacific Islander.[238] The study will recruit about 10,000 adults, ages 18-64, from across the U.S. and lead to new knowledge to improve cardiovascular health.

Individuals who have one or more heart attacks in their lifetime may experience faster long-term cognitive decline, according to an NIA-funded study. Using data from six NIH-funded longitudinal cohort studies of cardiovascular health, researchers found that heart attacks are an important risk factor for cognitive decline, even after someone has recovered from the heart attack itself.[239] These findings add to a growing amount of evidence pointing toward a link between heart and brain health. Additionally, the findings could

[236] Gracner T, et al. Science. 2024 Nov 29;386(6725):1043-1048. PMID: 39480913.
[237] Lampert R, et al. JAMA Cardiol. 2023 Jun 1;8(6):595-605. PMID: 37195701.
[238] https://www.nhlbi.nih.gov/news/2024/new-nhlbi-study-focuses-asian-americans-native-hawaiians-and-pacific-islanders
[239] Johansen MC, et al. JAMA Neurol. 2023 Jul 1;80(7):723-731. PMID: 37252710.

inform how health care providers monitor and discuss risk for cognitive decline in their patients after a heart attack.

Atrial fibrillation affects more than 2 million adults in the U.S. and is one of the most common types of arrhythmias (irregular heart rhythms). The risk of developing atrial fibrillation increases with age. That means that as the average age in the U.S. increases, more people will be affected by this condition. A predictive computer model developed by scientists supported by the NCATS Clinical and Translational Science (CTSA) Awards Program and NIA could help doctors decide when to start long-term monitoring to detect atrial fibrillation that may have been missed by a single test. To improve predictions, scientists reviewed information from 446,900 people who wore simple, single-lead electrocardiogram devices to develop a model to predict atrial fibrillation.[240] When testing the model against past data, the computer model alone was better at predicting atrial fibrillation within two weeks compared to models that relied only on such factors as a person's age, sex, heart rate variability, odd heartbeats, and heart rhythms.

In September 2022, NHLBI and the Foundation for NIH launched the AMP for Heart Failure.[241] The program—a public-private partnership between NIH, FDA, multiple biopharmaceutical and life sciences companies—will focus on heart failure with preserved ejection fraction, a condition in which the heart cannot meet the body's oxygen and nutrient needs. The program will use cutting-edge technologies, including digital measurements and SI analytic methods, to find novel proteins or genes that could alleviate this disease. Further, the program will use imaging, multi-omics in blood and other tissues, and deep clinical phenotyping to identify disease subtypes and novel biologic pathways and mechanisms underlying development and progression of heart failure with preserved ejection fraction, with the goal of turning the discovery of novel therapeutic targets into safe and effective treatments.

Launched in 1988, the Strong Heart Study investigates cardiovascular disease and its risk factors among American Indian men and women.[242] It is one of the largest epidemiological studies of American Indians ever undertaken. A 19-year review of data from more than 1,400 participants in the study found that more than 70 percent of American Indian young adults between the ages of 20 and 39, and 50 percent of American Indian teens between 15 and 19 have abnormal levels of lipids in the bloodstream.[243] This condition can be linked to plaque buildup in blood vessels and poses a significant risk factor for heart attacks and stroke.

Low-density lipoprotein, known as "bad" cholesterol, has a central role in cardiovascular disease. In 2024, NHLBI researchers visualized, for the first time, how the main structural protein of low-density lipoprotein binds to its receptor.[244] This process is important because it starts the clearing of low-density lipoprotein from the blood. These mechanistic insights might enable the future development of more effective, structurally informed treatments for high cholesterol by lowering low-density lipoprotein levels. Low-density lipoprotein cholesterol is often calculated using a formula rather than being directly measured,

[240] Gadaleta M, et al. NPJ Digit Med. 2023 Dec 12;6(1):229. PMID: 38087028.
[241] https://amphf.org/about/amp-hf-goals/
[242] https://www.nhlbi.nih.gov/science/strong-heart-study-shs
[243] Reese JA, et al. J Am Heart Assoc. 2024 Mar 19;13(6):e031741. PMID: 38445515.
[244] Reimund M, et al. Nature. 2025 Feb;638(8051):829-835. PMID: 39663455.

especially in clinical settings. Researchers at the NIH Clinical Center recently developed the Sampson-NIH equation for calculating the concentration of low-density lipoprotein cholesterol from the components of the standard lipid panel.[245] The equation was derived with samples run by the reference method of beta-quantitation and is recommended for clinical use by American College of Cardiology, the Canadian Cardiovascular Society, the Association for Diagnostics and Laboratory Medicine, the Canadian Society of Clinical Chemists, the European Society of Cardiology, and the Endocrine Society. It is currently being reported by the Mayo Medical Laboratories and LabCorp, as well as many hospitals throughout the world. Accurately measuring low-density lipoprotein cholesterol is important because it helps assess the risk of developing cardiovascular disease.

Improving Outcomes for Patients with Cardiovascular Disease

Chronic arsenic exposure among American Indians, who often live in rural communities that rely on private wells, has been associated with an increased risk of cardiovascular disease, diabetes, and lung, pancreas, and prostate cancers. However, little research has focused on developing and evaluating effective interventions to reduce exposures among private well users. NIEHS supported an intervention developed by the Strong Heart Water Study and led by Northern Great Plains American Indian Nations, which showed that installing kitchen faucet filters and implementing a digital health program reduced participants' arsenic levels by nearly half in American Indian households relying on well water.[246] Since public health interventions involving in-person visits can be costly and difficult to implement in rural areas, these findings could inform feasible arsenic mitigation programs among other private well users.

An NIH-supported clinical trial found that a daily statin medication reduced the risk of cardiovascular disease among people living with HIV.[247] The randomized, nonblinded, Phase 3 clinical trial known as Randomized Trial to Prevent Vascular Events in HIV found that statins, a class of cholesterol-lowering medications, may offset the high risk of cardiovascular disease in people living with HIV by more than one-third, potentially preventing one in five major cardiovascular events or premature deaths in this population.[248,249] This study highlights the evolving focus of HIV treatment towards addressing comorbidities such as cardiovascular disease, which are leading causes of morbidity and mortality as people with HIV live longer. Results are expected to influence future guidelines for managing cardiovascular health in the population of people with HIV.

Although statin has been used to treat cardiovascular disease in many patient groups with minimal side effects, it has been linked to autoimmune disease in certain populations. Researchers at the NIAMS intramural research program and colleagues discovered that, among American Indians, statin treatment might be associated with an unexpectedly higher rate of myositis, a group of inflammatory muscle diseases that cause inflammation and weakness in the muscles.[250] These findings provide a strong recommendation

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[245] Sampson M, et al. Clin Chem. 2024 Feb 7;70(2):399-402. PMID: 38006320.
[246] George CM, et al. Environ Health Perspect. 2024 Mar;132(3):37007. PMID: 38534131.
[247] https://www.niaid.nih.gov/news-events/daily-statin-reduces-risk-cardiovascular-disease-people-living-hiv-large-nih-study
[248] Grinspoon SK, et al. N Engl J Med. 2024 May 2;390(17):1626-1628. PMID: 37486775.
[249] Lu MT, et al. JAMA Cardiol. 2024 Apr 1;9(4):323-334. PMID: 38381407.
[250] Wei J, et al. Arthritis Rheumatol. 2022 Sep;74(9):1602-1603. PMID: 35333459.

to stop statin treatment for American Indian patients who test positive for myositis to reduce and prevent permanent muscle damage.

Home blood pressure monitoring is more convenient and effective than clinic-based monitoring in diagnosing and managing hypertension, especially in regions with reduced access to clinical care. However, there is limited evidence of the health and economic impacts of home monitoring. A recent study by NHLBI-supported researchers used cardiovascular disease modeling to estimate the long-term impact of adopting home blood pressure monitoring versus usual care on heart attack, stroke, and healthcare costs.[251] Compared with usual care, adopting home blood pressure monitoring was estimated to reduce heart attacks by 4.9 percent and stroke by 3.8 percent, as well as saving an average of $7,794 in healthcare costs per person over 20 years.

Many older adults take low-dose aspirin daily to prevent stroke. However, little is known about the side effects of daily low-dose aspirin, like potential bleeding in the brain following falls. Researchers examined the risks of ischemic stroke—caused when a vessel supplying blood to the brain is obstructed—and intracranial bleeding among healthy older people receiving daily low-dose aspirin. The study found that there was a significant risk of bleeding in the brain from head trauma such as falls, with daily low-dose aspirin but no significant reduction in stroke.[252] These findings suggest that low-dose aspirin may have no role for the primary prevention of stroke and that caution should be taken with use of low-dose aspirin in older persons prone to head trauma, such as from falls.

Chronic Pain

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 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 2023 National Health Interview Survey show that 24.3 percent of adults—around 50 million people—had chronic pain and 8.5 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.[253]

Pain Research

"Placebo analgesia" is when an individual experiences pain relief after receiving a treatment that has no active pain-relieving chemical ingredients, simply because they expect it to work. Previous studies in human imaging experiments showed some brain regions involved in placebo analgesia, but they lacked the precision needed to show what was happening in those brain regions. An NINDS-supported research team showed in precise detail, down to the cellular level in mice, that there is a placebo analgesia circuit

[251] Li Y, et al. Am J Prev Med. 2023 Nov;65(5):775-782. PMID: 37187442.
[252] Cloud GC, et al. JAMA Netw Open. 2023 Oct 2;6(10):e2340464. PMID: 37494038.
[253] https://www.cdc.gov/nchs/products/databriefs/db518.htm

from the anterior cingulate cortex to the pons region of the brainstem to the cerebellum in the back of the brain.[254] Understanding this precise circuit might one day lead to specific circuit level therapies for pain in humans.

Orofacial pain, such as a toothache or migraine, can hinder daily activities like eating and tooth-brushing and affects as much as 12 percent of the population. Some patients use opioid-based pain relievers, which carry a risk of misuse. Understanding how facial nerves process pain signals could help scientists find safer and more effective pain interventions. Using an imaging technique to visualize pain signals in facial nerves, NIDCR intramural researchers identified a protein that enhances neurons' responses to painful stimuli.[255] By therapeutically blocking this protein in animal models, the neurons involved in pain signaling were blunted, suggesting that this inhibitor could be used as a safer alternative to opioid-based pain relievers.

Temporomandibular disorders (TMDs) are a group of more than 30 conditions that cause pain and dysfunction in the jaw joint and muscles that control jaw movement. The NIDCR-led Orofacial Pain: Prospective Evaluation and Risk Assessment study was the first and only prospective, longitudinal study of TMDs to enroll and monitor over 4,000 people during a 5-year period. It identified risk factors, signs, symptoms, genetic factors, and environmental events that contribute to the development and chronic nature of painful TMDs. The study also aimed to understand factors that predict the transition from acute to chronic TMDs, as well as the development of chronic overlapping pain conditions, including headache, low back pain, irritable bowel syndrome, and widespread body pain.[256] A recent analysis of study samples revealed critical epigenetic signals that can predict the development of chronic TMD symptoms. Another recent analysis of study data demonstrated how a multisystem patient assessment can identify signs and symptoms indicative of TMDs before their onset.[257]

The Temporomandibular disorder Collaborative for Improving Patient-Centered Translational Research Initiative, also spearheaded by NIDCR, and in partnership with NIAMS, NIBIB, NINDS, and others, aims to advance TMD basic and clinical research, research training, and translation to evidence-based treatments and improved clinical care.[258] Nine planning grants were awarded in 2023 to enable institutions to develop the necessary partnerships, infrastructure, and capabilities to address the goals of the collaborative. Examples include integrating basic and clinical research efforts and training to improve clinical care, etiologic mechanisms for TMDs, and patient-centered research and outcomes.

Pain can arise from different causes, including inflammation, nervous system injury, or tissue damage; and though the way the body senses these different types of pain vary, current pain relief medications focus on relatively few drug targets. A goal of the Common Fund's Illuminating the Druggable Genome program was to catalyze research that could facilitate the discovery of new drug targets. Research supported by the program used SI and data on genes, proteins, and RNA molecules from 14 databases and publications to prioritize drug targets for human genes associated with 17 types of pain.[259] Using this approach, the study

[254] Chen C, et al. Nature. 2024 Aug;632(8027):1092-1100. Epub 2024 Jul 24. PMID: 39048016.
[255] Hu, M., et al. Cell Rep. 2022 Mar 8;38(10):110458. PMID: 35263573.
[256] Chen H, et al. Pain. 2023 May 1;164(5):1027-1038. Epub 2022 Oct 19. PMID: 36661844.
[257] Ao X, et al.. Pain. 2024 May 1;165(5):1060-1073. Epub 2023 Nov 28. PMID: 38015635.
[258] https://www.nidcr.nih.gov/grants-funding/research-funded-by-nidcr-extramural/tmd-impact
[259] https://commonfund.nih.gov/idg/highlights/identifying-targets-pain-medication-artificial-intelligence

identified 13 potential targets for migraine drug development and four potential drug targets for rheumatoid arthritis, paving the way for more chronic pain treatment options.

The Common Fund, in DPCPSI within the NIH OD, also supports the Acute to Chronic Pain Signatures program, which aims to develop a set of biomarkers that provide "signatures" to predict if chronic pain is likely to develop or be resolved after acute pain, like an injury or after a surgery. Researchers supported by this program published a paper which included a review of what is understood about potential markers of chronic pain and provided an overview of how the Common Fund program aims to expand on that knowledge, paving the way for personalized pain treatment strategies.[260,261]

Uncovering the biomechanical processes underlying human touch and sensation is critical to understanding this essential human function and key to discovering potential new approaches to treating pain. NCCIH-supported research is contributing to a growing understanding of the mechanoreceptive ion channel PIEZO2 (specialized membrane protein that converts physical forces, like touch, into electrical signals that the brain can sense) and its role in touch in both mice and humans.[262] While the study focus on the role of the membrane ion channel for sexual function, the results are more broadly applicable towards the molecular underpinning of touch and potentially provide clues to new therapeutic avenues for managing chronic pain.

Several clinical studies seek to understand the fundamentals of chronic pain and associated therapies. Building on the success of Implementing Genomics in Practice Network, established in 2013, NHGRI launched the second phase in 2018, focused on a Pragmatic Clinical Trials Network.[263] The network comprises five multi-site Clinical Groups and one Coordinating Center involving various settings and populations to conduct pragmatic clinical trials of genomic medicine interventions. One of the trials is studying the use of pharmacogenomics in treating post-surgical pain, chronic pain, and depression.[264,265,266] Other trials are studying the effects of returning genomic risk information to hypertensive patients and their primary care providers,[267] the impact of genetics in the risk of kidney failure,[268] and genotype-guided antiplatelet therapy in percutaneous coronary intervention.[269] These trials will allow the assessment of the clinical utility and cost-effectiveness of genomic medicine interventions in various clinical settings and are instrumental in determining the clinical utility and cost-effectiveness of genomics-based approaches across many healthcare environments, including therapies for chronic pain.

Back pain is one of the most common reasons people seek medical help or miss work and is a leading cause of disability worldwide. NCCIH-supported scientists conducted a study of adults in the U.S. with

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[260] https://commonfund.nih.gov/pain/highlights/a2cps-team-publishes-candidate-markers-chronic-pain
[261] Sluka KA, et al. Pain. 2023 Sep 1;164(9):1912-1926. Epub 2023 Jun 15. PMID: 37326643.
[262] Lam RM, et al. Science. 2023 Aug 25;381(6660):906-910. Epub 2023 Aug 24. PMID: 37616369.
[263] https://www.genome.gov/Funded-Programs-Projects/Implementing-Genomics-in-Practice-IGNITE-Pragmatic-Clinical-Trials-Network
[264] Cavallari LH, et al. Clin Transl Sci. 2022 Oct;15(10):2479-2492. Epub 2022 Aug 4. PMID: 35899435.
[265] Skaar TC, et al. Clin Transl Sci. 2024 Aug;17(8):e70005. PMID: 39177194.
[266] Hines LJ, et al. Clin Transl Sci. 2024 Jun;17(6):e13822. PMID: 38860639.
[267] Eadon MT, et al. Contemp Clin Trials. 2022 Aug;119:106813. Epub 2022 Jun 1. PMID: 35660539.
[268] Nadkarni GN, et al. JAMA Netw Open. 2022 Mar 1;5(3):e221048. PMID: 35244702.
[269] Beitelshees AL, et al. J Am Heart Assoc. 2022 Feb 15;11(4):e024159. Epub 2022 Feb 12. PMID: 35156424.

chronic severe back pain and showed that nearly 21 percent did not receive treatment for at least three months and that socioeconomic factors played a role.[270] Findings from studies like these highlight the need for continued support of research to address pain and treatment of pain, especially by reducing barriers to care.

The NIH Helping to End Addiction Long-term® Initiative

Pain, especially chronic pain, contributed to the opioid crisis and people living with pain need effective, non-addictive pain treatments. The Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative® was launched in 2018 as an aggressive NIH-wide effort to provide scientific solutions to the national opioid overdose crisis.[271] The initiative is jointly managed by NIDA and NINDS in close collaboration with other NIH ICOs; and funds around 1,800 projects nationwide focusing on both improving prevention and treatment for opioid misuse and addiction and understanding, managing, and treating pain. NINDS leads the pain management research programs within the HEAL Initiative, in collaboration with 15 other NIH ICOs. This includes programs to advance the discovery and development of new, non-addictive alternatives to opioids to treat acute and chronic pain conditions, programs to develop biomarker signatures to assess pain objectively, and clinical research that seeks to improve pain care in populations with higher health burdens.

NIAMS leads two HEAL programs aimed at reducing pain. The Restoring Joint Health and Function to Reduce Pain Consortium supports research to address the problem of joint pain as a contributing factor for opioid use. The consortium supports research to map and compare the network of sensory nerves in the temporomandibular (jaw) joint and the sensory nerves of the knee. Researchers are working to understand how these types and patterns of sensory nerves in joints change with disease and aging. This work will help inform effective strategies to decrease the use of opioids by developing more precise ways to reduce joint pain, limit joint deterioration, and restore healthy joints. The Back Pain Consortium Research Program takes a patient-centered approach to address the need for personalized therapies for chronic low back pain. Under the program, the Biomarkers for Evaluating Spine Treatments clinical trial measures the effectiveness of existing chronic low back pain treatments to determine what patient characteristics are associated with the best outcomes for each treatment.

The NIH HEAL Initiative also supports studies that aim to develop biomarkers for pain. For the first time, researchers, supported by the Brain Research through Advancing Innovative Neurotechnologies Initiative and HEAL Initiative, have recorded brain activity related to pain directly from individuals suffering from chronic pain.[272] In four participants, three experiencing post-stroke pain and one with phantom limb pain following amputation, the researchers analyzed the participants' pain ratings alongside brain activity data using machine learning and identified brain activity biomarkers of chronic pain. The results offer a promising path toward future therapies that target specific brain circuits to alleviate pain symptoms. In another study, investigators studied whether brain activity patterns can accurately classify an individual's

[270] Feldman DE and Nahin RL. J Pain. 2024 Nov;25(11):104637. Epub 2024 Jul 20. PMID: 39033901.
[271] https://heal.nih.gov/
[272] Shirvalkar P, et al. Nat Neurosci. 2023 Jun;26(6):1090-1099. Epub 2023 May 22. PMID: 37217725.

sensitivity to pain.[273] Researchers measured two brain signals in 150 healthy adults with temporary jaw pain and used machine learning to develop a model to predict pain sensitivity levels. The model was highly reliable and consistent across different testing methods, suggesting that these brain activity markers could help identify who might develop chronic pain, which has the potential to improve early diagnosis and treatment strategies.

NIDA leads two programs under the HEAL initiative aimed at reducing opioid-related harms to treat chronic pain. The Integrative Management of chronic Pain and Opioid Use Disorder for Whole Recovery program develops and tests combined interventions such as psychotherapy, medications, exercise, and pain self-management. These interventions are embedded within specific health care system settings and with a holistic, whole-patient focus. The network collaborates with individuals with lived experience and public/private partners to examine implementation factors such as financing and organizational barriers. The Multilevel Interventions to Reduce Harm and Improve Quality of Life for Patients on Long Term Opioid Therapy program supports research to reduce harm and improve the quality of life of people with chronic pain who take opioids long-term. This research develops interventions for patients as well as strategies for health care providers and health systems who help manage the care of these patients.

The NIH HEAL Initiative supports small businesses focused on developing innovative, non-opioid technologies and products to enhance pain management. For example, HEAL supported researchers to develop a new pain-relief drug, SRP-001, that could be a safer alternative to opioid medications, non-steroidal anti-inflammatory drugs (like ibuprofen), and acetaminophen. Early tests of SRP-001 show that it provides similar pain relief without the liver damage that acetaminophen overdose can cause, and that it is safe and well-tolerated in humans.[274] Another group of HEAL investigators developed a new pain medication called EC5026 that works by blocking an enzyme that breaks down natural pain-relieving compounds in the body which allows them to last longer.[275] Early clinical trials based on these findings showed EC5026 was well tolerated with no serious side effects. A third group of investigators conducted investigational new drug-enabling studies for AFA-281, a new pain therapeutic for neuropathic pain that dually targets a calcium channel and inhibits a key enzyme.[276] Early studies in humans showed that the drug was safe and well tolerated, and researchers are now preparing for larger trials to test this new medication on individuals with chronic neuropathic pain.

Researchers supported by NIAMS, through the NIH HEAL Initiative, received small business funding to develop a rapid, inexpensive, and quantitative high-throughput platform with potential for discovering new pain therapeutics. They tested this platform in an *in vitro* osteoarthritis “pain-in-dish” model and validated the platform’s performance by successfully identifying drugs with known neuron-inhibiting properties. They also discovered that six inhibitors of the intracellular mitogen-activated protein kinase

[273] Chowdhury NS, et al. JAMA Neurol. 2025 Mar 1;82(3):237-246. PMID: 39869323.
[274] Bazan HA, et al. Sci Rep. 2024 May 15;14(1):11103. PMID: 38750093.
[275] Schmidt, W.K., et al. Clin Transl Sci. 2024 Sep;17(9):e70033. PMID: 39300734.
[276] https://www.afasci.com/index.php/drug-discovery

signaling pathway reversed neuron hyperexcitability caused by inflammatory factors.[277] These findings suggest that the signaling pathway could be a drug target for treating chronic pain.

Collaborations and Partnerships

To get a better understanding on the utilization of treatment options for pain management, NCCIH and CDC scientists collaborated on a study to characterize treatments among commercially versus Medicaid-insured adults with incident episodes of chronic pain. An analysis of medical claims data suggests that adults experiencing new episodes of chronic pain may have differential access to all treatment options—including type, pattern, and timing—based on the type of health insurance they have. These results suggest differential access to evidence-based treatment options early during care and identify opportunities to align coverage and reimbursement policies with current practice guidelines.[278]

The NIH-DoD-VA Pain Management Collaboratory is comprised of 16 large-scale, multisite, pragmatic clinical trials that focus on implementation and evaluation of nonpharmacological approaches for the management of pain and common co-occurring conditions in military and veterans healthcare systems. NCCIH within NIH, Department of Defense (DoD), and the Department of Veterans Affairs (VA) are the lead funders. In 2023, the Collaboratory issued a funding solicitation for research applications to conduct efficient, large-scale pragmatic clinical trials and/or implementation science demonstration projects on nonpharmacologic approaches to pain management and other comorbid conditions. The funding solicitation is also supported by NINR and two DPCPSI offices within the NIH OD, ODP and OBSSR. The Collaboratory established a Coordinating Center that provides national leadership and technical expertise for all aspects of health care system-focused research, including assistance to the eventual awardees.[279]

Rural populations, including Tribal Nations, are disproportionally affected by chronic pain and the opioid crisis, partially due to limited access to healthcare services. Adhering to HHS and NIH policy, Tribal consultation, an official government-to-government interaction, occurs before any NIH action is taken that will significantly impact AI/AN Tribal Nations and populations. Tribal consultation emphasizes trust, respect, and shared responsibility. It is a free exchange of information and opinions among NIH and Indian Tribes that leads to mutual understanding and comprehension. The NIH HEAL Initiative, in collaboration with THRO, initiated a Tribal consultation to engage Tribal leaders in discussions on integrating traditional and cultural practices into AI/AN-led research in addressing the opioid crisis and supporting new strategies to improve chronic pain management.[280]

Cystic Fibrosis

Cystic fibrosis (CF) is an inherited disease of the secretory glands, which include glands that make mucus and sweat, and 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 and blocks the airways of the lungs and various ducts in other organs, causing the characteristic signs and symptoms of CF. This buildup of

[277] Liu PW, et al. Pain. 2024 Apr 1;165(4):922-940. Epub 2023 Nov 14. PMID: 37963235.
[278] Bohm MK, et al. J Pain. 2024 Dec;25(12):104667. Epub 2024 Sep 11. PMID: 39271034.
[279] https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-24-004.html
[280] https://dpcpsi.nih.gov/thro/tribal-consultations/nih-heal-initiative

mucus also makes it easy for bacteria to grow, leading to repeated, serious infections. Over time, these infections can severely damage the lungs and other organs.[281]

People who have CF inherit two faulty genes (one from each parent) of a protein called cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is important because it spans the membranes of cells and regulates the concentration of the chloride ion—a component of salt—in cells, which in turn helps to maintain the balance of salt and water on surfaces such as in the lungs. With this balance disrupted due to a dysfunctional *CFTR* gene, the mucus covering cells become thick, resulting in the wide range of CF symptoms. CF affects about 35,000 Americans; however, it is most common among people of Northern European descent.[282,283] More than ten million Americans are carriers of a faulty *CFTR* gene, although many do not know it as one faulty gene is not sufficient to cause disease.

An early-stage clinical trial has begun to evaluate bacteriophage therapy for adults with CF who are infected with *Pseudomonas aeruginosa* in their lungs.[284] *Pseudomonas aeruginosa*, a serious and sometimes deadly bacterium frequently acquired in healthcare settings, is the most common bacterial cause of breathing difficulties in CF. The trial aims to determine the safety and efficacy of bacteriophage therapy in reducing lung bacteria. Bacteriophages are viruses that can kill or neutralize specific bacteria while leaving non-target bacteria and human cells unharmed. For more than a century, researchers have considered the potential use of bacteriophages as therapeutics, theorizing that mixtures of bacteriophages might be used on their own, or in conjunction with antibiotics, to treat bacterial infections—especially those resistant to antibiotics. The trial, starting with a Phase 1b and progressing to Phase 2, will assess various outcomes including safety, lung function changes, and quality of life impacts. If successful, this therapy would have to complete larger Phase 3 trials before potentially being available to CF patients to help alleviate breathing difficulties.

The ultimate goal is to develop a therapy that corrects the faulty CFTR protein so that CF patients live normal lives. In a recent study, NHLBI researchers optimized gene editing technology to correct a gene mutation that causes most CF.[285] The technique, called prime editing, is a variation of CRISPR technology that makes precise and targeted modifications to DNA with minimal off-target errors. Researchers were able to successfully correct the gene to 58 percent in a bronchial epithelial cell line grown in the laboratory and to 25 percent in patient-derived airway epithelial cells (cells removed from a CF patient and grown in the laboratory). More importantly, in the patient cells, researchers were also able to restore function of the CFTR protein to more than 50 percent compared to cells without gene correction—similar to what the best current therapeutic drugs can achieve. These results are a promising step towards a future gene therapy that can successfully treat CF patients.

[281] https://www.nhlbi.nih.gov/health/health-topics/topics/cf
[282] https://www.cdc.gov/cystic-fibrosis/about/index.html
[283] https://medlineplus.gov/genetics/condition/cystic-fibrosis/#inheritance
[284] https://www.niaid.nih.gov/news-events/nih-supported-clinical-trial-phage-therapy-cystic-fibrosis-begins
[285] Sousa AA, et al. Nat Biomed Eng. 2025 Jan;9(1):7-21. PMID: 38987629.

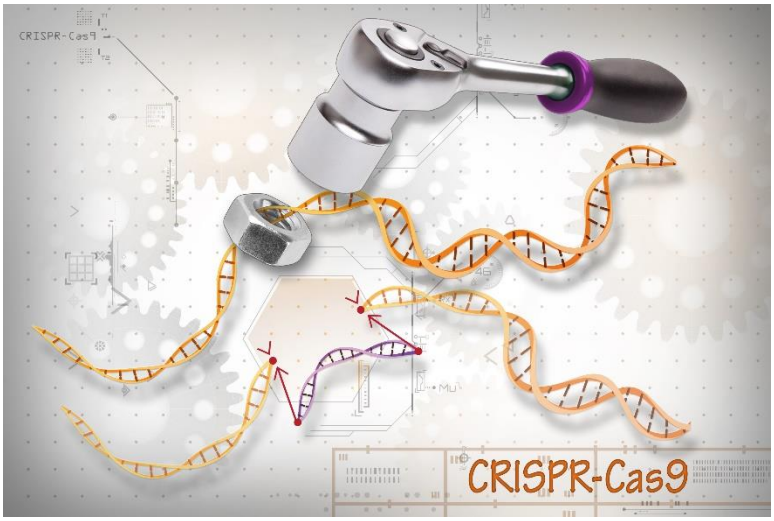


Figure 18. CRISPR-Cas9 is a customizable tool that lets scientists cut and insert small pieces of DNA at precise areas along a DNA strand. The tool is composed of two basic parts: the Cas9 protein, which acts like the wrench, and the specific RNA guides, CRISPRs, which act as the set of different socket heads. These guides direct the Cas9 protein to the correct gene, or area on the DNA strand, that controls a particular trait. Credit: Ernesto del Aguila III, NHGRI/NIH

Dental, Oral, and Craniofacial Diseases

Dental, oral, and craniofacial diseases—including tooth decay and periodontal (gum) disease, cancers of the oral cavity, and temporomandibular joint disorders—remain among the most common chronic conditions nationwide. For example, untreated cavities affect roughly one in five U.S. adults ages 20 to 64 and one in ten adolescents aged 12 to 19.[286] Beyond pain and disability, dental, oral, and craniofacial conditions can be fatal: NCI projects 12,230 deaths from oral cavity and pharynx cancers in 2024 alone, despite significant gains in early detection and therapy.[287] NIH supports a research portfolio dedicated to understanding and treating dental, oral, and craniofacial diseases and NIDCR is the lead IC for scientific research in this area. Considering that the biological processes underpinning dental, oral, and craniofacial diseases and conditions are common across a wide variety of diseases and conditions, many other NIH ICs also contribute to NIH's portfolio in this area.

Research to Improve Dental, Oral, and Craniofacial Health

Cleft palate is a common facial birth defect that occurs when the developing tissues that normally join to form the roof of the mouth (or palate) do not fuse properly, leaving an opening (or cleft). This opening may affect eating and breathing and can cause speech delays. A landmark international trial compared cleft-palate repair at 6 months versus 12 months of age in infants with isolated cleft palate. Children who underwent the earlier procedure showed significantly lower rates of velopharyngeal insufficiency (structural dysfunction that affects speech) and clearer speech by age 5 years.[288] The study confirmed that

[286] https://www.cdc.gov/oral-health/about/cavities-tooth-decay.html
[287] https://seer.cancer.gov/statfacts/html/oralcav.html
[288] Gamble C, et al. N Engl J Med 2023;389(9):795-807. PMID: 37646677.

large, multicenter surgical trials are feasible in craniofacial disorders and supplies the first high-quality evidence to guide global timing standards.

Tooth decay is the most common chronic disease of childhood, affecting nearly 46 percent of children in the U.S. Left untreated, cavities can put children at risk for chronic pain, impaired development, and long-term oral and overall health problems. Current treatments for severe tooth decay rely on restoration and tooth extraction, which are expensive, require the use of anesthesia, and may require further treatment. NIDCR-sponsored researchers investigated the efficacy of an easy-to-use, readily accessible, and already FDA-cleared topical liquid, silver diamine fluoride, for the treatment of severe tooth decay. The Phase 3 trial tested a topical silver diamine fluoride solution as a non-invasive treatment to halt early childhood cavities. An interim analysis of 599 preschoolers found that a single application arrested 54 percent of active cavities versus 21 percent with placebo, leading the data safety board to stop the study early due to the clear indications of effectiveness.[289] The inexpensive, shelf-stable liquid can be applied quickly in schools, primary-care settings, and in geriatric settings for individuals with tooth decay on root surfaces by non-dentists, making it especially suited to underserved communities where dental anesthesia and restorations are impractical.

It is commonly believed that because young children lose their baby teeth, they do not need regular cleanings or cavity treatment. However, without regular dental care, the bacteria that cause tooth decay can remain in the mouth and attack emerging permanent teeth. An NIDCR funded cluster-randomized trial in 18 pediatric practices tested whether primary-care clinicians could boost early dental attendance.[290] Training physicians to discuss oral health, perform brief oral exams, and provide parents printed referrals increased odds of completed dental visits by 34 percent within a year compared with standard well-childcare. Parents reported greater awareness of cavity risk and a stronger commitment to timely check-ups. Integrating these low-cost steps into routine wellness visits could narrow differences across groups in untreated tooth decay, the Nation's most common chronic childhood disease.[291]

Periodontal (gum) disease can lead to loss of the tissue and bone that hold teeth in place. Gingival epithelial cells are the cells that form the outermost layer of the gums, or gingiva, which are the tissues surrounding and protecting the teeth. Typically, when a toxin, virus, or bacteria breaches this barrier, the immune system's surveillance cells detect that change and respond to eradicate the threat, often by triggering inflammation. New mechanistic insights reveal that gingival epithelial cells act as active sentinels rather than passive barriers. Using single-cell transcriptomics and mouse infection models, NIDCR funded researchers showed that microbial sensing by these cells triggers interleukin-23 release, initiating a local inflammatory cascade that can escalate periodontal lesions.[292] Targeting epithelial interleukin-23 signaling offers a promising route to halt early gingival inflammation before it progresses to the tissue and bone loss characteristic of chronic periodontitis.

[289] Fontana M, et al. Pediatr Dent 2024;46(1):8-12. PMID: 38449039.
[290] Nelson S, et al. JAMA Netw Open 2024;7(7):e2418217. PMID: 38980678c.
[291] https://www.nidcr.nih.gov/news-events/nidcr-news/2024/dental-visits-increase-support-pediatric-providers
[292] Kim TS, et al. Immunity 2024;S1074-7613(24):00096-7. PMID: 38513665.

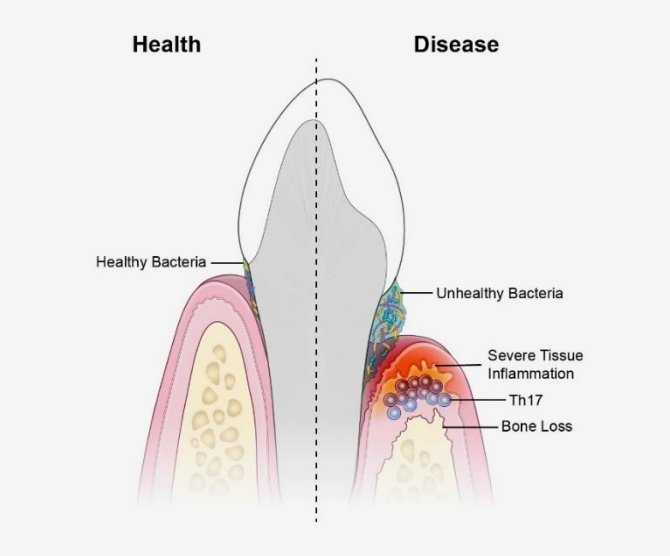


Figure 19. Periodontal disease is driven by a complex interaction between unhealthy bacteria and immune cells, such as T helper 17 immune cells, which are though to play a role. Credit: NIDCR/NIH

Biofilms are assorted microbial communities characterized by their ability to adhere to surfaces, like teeth, and each other. Disruptions in the balance of the bacteria found in oral biofilms can lead to gum disease. Bacteriophages, or "phages" for short, are a group of viruses that exclusively infect and can be targeted to kill bacteria. An important obstacle to utilizing phages to selectively re-balance the oral microbiome has been difficulty in penetrating the biofilm microenvironment and accessing the phage's target bacteria. NIDCR funded researchers discovered that the oral bacterium *Capnocytophaga gingivalis,* with its natural gliding and swarming movements, can ferry phages through dense dental biofilms that normally exclude these viruses. Using time-lapse microscopy and fluorescently labeled phage, the team showed that the bacterial carve tunnels into the extracellular matrix, creating flow paths that speed phage particles up to ten-fold compared with passive diffusion.[293] This swarm-assisted delivery mechanism offers a blueprint for engineering biofilm-busters to enhance non-antibiotic treatment of dental cavities and periodontitis.

Over the last few decades, resin-based composites have become the standard filling material used to treat tooth decay while conserving tooth structure. Drawing on electronic health records from 37,000 patients in the National Dental Practice-Based Research Network, NIDCR supported investigators conducted the largest analysis of posterior resin-based composite restorations to date. Overall, 16% of these fillings failed during follow-up, with 20% of the failures occurring within 1 year and another 54% having failed between 1 and 5 years after placement. A high percentage of failures were due to secondary tooth decay, highlighting the importance of ongoing tooth decay risk assessment and management after dental filling placement.[294] These findings highlight the importance of durable materials that minimize tooth decay recurrence.

Capacity Building and Community Engagement

[293] Ratheesh NK, et al. Microbiol Spectr 2023;11(4):e00937-23. PMID: 37358420.
[294] Thyvalikakath T, et al. J Dent 2024;141:104831. PMID: 38190879.

Building and maintaining capacity for research is vital to advancing groundbreaking research on dental, oral, and craniofacial diseases. The NIDCR-supported Dental, Oral, and Craniofacial Tissue Regeneration Consortium supports the development of regenerative products for clinical application in dental and craniofacial medicine. The Consortium aims to accelerate translation by forming a national network of interdisciplinary teams that address barriers in regulatory science, product development, and commercialization. Through its translational research hubs, the consortium advances therapies for periodontal defects, temporomandibular joint dysfunction, tooth remineralization, and reduced salivary gland function.[295,296]

FaceBase 3 continues to serve as an open, NIH-funded data platform that unifies genomic, imaging, and phenotypic datasets on craniofacial and dental biology. The platform's intuitive interface lets researchers query over 1,000 data sets across anatomical regions (including teeth and gums), disease states, and multiple species, supporting both discovery science and translational studies. Rigorous metadata standards, built-in visualization tools, and cloud-based workflows promote interoperability with other public repositories and make complex, multidimensional files immediately usable by investigators of varied expertise. By lowering technical barriers to collaboration, FaceBase accelerates progress toward understanding congenital anomalies and developing new diagnostics and therapies.[297]

To strengthen prevention in everyday practice, NIDCR and the American Dental Association launched the *Putting Prevention into Action* webinar series, focusing on community water fluoridation and school-based sealant programs.[298] The first of the two 2024 sessions featured a panel discussion on current research regarding the effectiveness of community water fluoridation, the relationship between fluoride and neurocognitive development, and future directions of fluoride-related research. The second webinar featured a panel discussion on the current landscape of dental sealant uptake and implementation, opportunities and challenges for school-based programs, parental concerns and education, and guidance for providers on evaluating the validity of published research. By pairing pragmatic case studies with live question and answer session, the series equips clinicians, public-health officials, and educators worldwide, offering evidence updates, implementation toolkits, and continuing-education credits to translate proven preventive interventions into measurable oral-health gains.

Diabetes

Diabetes is the seventh leading cause of death in the U.S. It is a disease that occurs when a person's blood glucose (sugar) level 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 beta cells of the pancreas, helps glucose get 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 40 million Americans have

[295] https://www.nidcr.nih.gov/about-us/timeline/doctrc
[296] https://doctrc.org/
[297] https://www.facebase.org/about/
[298] https://www.nidcr.nih.gov/news-events/events/2024/putting-prevention-action-community-water-fluoridation-webinar

diabetes, and more than two in five adults have a condition called prediabetes, which puts them at elevated risk for developing diabetes.[299] Diabetes has serious health complications including heart disease, stroke, blindness, kidney failure, and lower-extremity amputations.

The most common types of diabetes are type 1, type 2, and gestational diabetes. In 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 from an outside source every day to stay alive. In 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 is a serious autoimmune condition that often begins in childhood, and researchers supported by NIH are working across disciplines to prevent the disease, understand its triggering factors, manage complications, and improve quality of life for those affected. TrialNet is an NIDDK-led clinical trials network that conducts trials of agents to prevent clinical diagnosis of type 1 diabetes in high-risk individuals and to slow disease progression in the newly diagnosed.[300] Landmark research conducted by TrialNet led to the November 2022 FDA approval of teplizumab as the first early, preventive treatment that can delay clinical diagnosis of type 1 diabetes in people ages eight and older.[301] Other research by TrialNet is shedding light on possible prevention therapies such as the autoimmune drug abatacept, which was shown to preserve insulin production and improve long-term blood glucose control in individuals who were newly diagnosed.[302] TrialNet has one ongoing prevention trial,[303] as well as several planned trials, which require screening large numbers of people to identify those with autoimmune risk factors.

While early intervention trials are showing promise in delaying or preventing disease onset, researchers are also investigating the environmental factors that may trigger type 1 diabetes. NIDDK's The Environmental Determinants of Diabetes in the Young is a long-term study that enrolled over 8,000 newborns to identify environmental triggers of type 1 diabetes in genetically susceptible individuals.[304]

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[299] https://www.cdc.gov/diabetes/about/index.html
[300] https://www.trialnet.org/
[301] https://www.trialnet.org/events-news/blog/trialnet-research-leads-fda-approval-first-drug-delay-type-1-diabetes
[302] Russell WE, et al. Diabetes Care. 2023 May 1;46(5):1005-1013. PMID: 36920087.
[303] Libman I, et al. Diabetes Care. 2023 Nov 1;46(11):2035-2043. PMID: 37708415.
[304] https://teddy.epi.usf.edu/

The study followed participants until they developed type 1 diabetes or turned 15 years of age and collected dietary and health data as well as stool, blood, and other samples. A significant "omics" effort, including metabolomics, proteomics, and studies of the microbiome and virome, is addressing questions related to the cause and course of autoimmunity and type 1 diabetes. Analyses of thousands of blood samples from children have identified proteins that can predict early stages of the disease, which could lead to improved methods to detect autoimmunity before clinical disease onset and help determine who is likely to progress to type 1 diabetes.[305] Continued analyses of study data and samples are expected to yield critical insights into the type 1 diabetes disease process and uncover environmental contributors to disease onset.

Building on this understanding of early risk, researchers are examining how broader social and environmental factors may influence disease management in children already living with type 1 diabetes. The Collaborative Centers in Children's Environmental Health Research and Translation turn research results into tangible tools, strategies, interventions, messages, and materials to protect children from harmful environmental exposures and improve health.[306] An example of this kind of work is a recent study in which NIEHS researchers looked at management of type 1 diabetes; specifically, whether family and neighborhood attributes influence the management of blood glucose levels in young adolescents.



Figure 20. A finger stick helps patients with diabetes take control of their blood sugar levels. Credit: Darryl Leja, NHGRI/NIH

In addition to early prevention and management, NIH is also investing in research to address long-term complications of type 1 diabetes that can affect the brain, heart, kidneys, and overall quality of life. NIDDK supports consortia focused on combating type 1 diabetes complications to improve health outcomes in people with the disease, such as research to understand the neurocognitive impact of type 1 diabetes in children to inform strategies to mitigate the risk of developing neurocognitive complications in later life. Researchers have also identified mechanisms that promote the development of cardiovascular disease in

[305] Nakayasu ES, et al. Cell Rep Med. 2023 Jul 18;4(7):101093. Epub 2023 Jun 29. PMID: 37390828.
[306] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-20-001.html

people with type 1 diabetes toward developing cardiovascular prevention and treatment strategies as well as identifying risk mitigation strategies for using in type 1 diabetes agents shown to be cardioprotective in type 2 diabetes.[307] Additionally, researchers are working to identify factors that restore awareness of hypoglycemia in adults with type 1 diabetes and impaired awareness of hypoglycemia toward tailoring treatment approaches and addressing clinically significant questions to improve diabetic foot ulcer healing and prevent amputations.[308] NIDDK also supports the landmark Epidemiology of Diabetes Interventions and Complications Study, which recently showed that a personalized approach to kidney disease screening for people with type 1 diabetes may reduce the time that chronic kidney disease goes undetected, providing the basis for the first evidence-based kidney screening model for people with the disease.[309]

Complementing these efforts to prevent and reduce complications, researchers are advancing technologies like artificial pancreas systems to help people with type 1 diabetes manage their blood glucose more effectively. 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 to deliver the insulin—that work together to mimic how a healthy pancreas controls blood glucose. 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 most new artificial pancreas devices currently on the market. For example, positive clinical trial results led to FDA approval of the iLet bionic pancreas device for both children and adults.[310,311] The device itself was derived from a system originally developed with NIDDK support. Other research demonstrated that the Control-IQ hybrid artificial pancreas device, developed with NIDDK support and already FDA approved for people ages six and older, also improved blood glucose control in young children between ages two and five with type 1 diabetes—a particularly challenging group when it comes to managing blood glucose levels.[312] Continued artificial pancreas research is important to give people with type 1 diabetes 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. Decades of NIH-supported research, including research conducted by the NIDDK and NIAID co-led Clinical Islet Transplantation Consortium, led to the June 2023 landmark FDA approval of a cellular islet transplantation therapy for people with type 1 diabetes whose disease cannot be managed using current therapies.

Islet transplant recipients must take long-term immunosuppressants to prevent the body from attacking the transplanted islets, and such medicines may cause serious side effects. Therefore, researchers are looking for ways to prevent islet transplant rejection without the need for long-term immunosuppressants,

[307] https://www.care-t1d.org/
[308] https://diabeticfootconsortium.org/
[309] Perkins BA, et al. Diabetes Care. 2022 Dec 1;45(12):2943-2949. PMID: 36321737.
[310] Bionic Pancreas Research Group et al. N Engl J Med. 2022 Sep 29;387(13):1161-1172. PMID: 36170500.
[311] https://www.fda.gov/news-events/press-announcements/fda-clears-new-insulin-pump-and-algorithm-based-software-support-enhanced-automatic-insulin-delivery
[312] Wadwa RP, et al. N Engl J Med. 2023 Mar 16;388(11):991-1001. PMID: 36920756.

such as by encapsulating islets with a material that protects them from immune system attack. Significant progress has been made toward developing encapsulated human islets, like identification of hydrogels and microgels for coating the islets;[313] development of animal models for studying their efficacy;[314] and development of different approaches to transplant the islets.[315] Such advances, in parallel with research toward generating and preserving sufficient numbers of islets for implantation, continue to yield knowledge necessary to further develop islet replacement therapy as a cure for type 1 diabetes.

Type 2 Diabetes Research

Type 2 diabetes is a complex and growing public health challenge driven by biological, environmental, and behavioral factors, but recent research supported by NIH is shedding light on innovative ways to treat, prevent, and better understand the disease. In type 2 diabetes, because of inefficiency in the body's use of the hormone insulin and a relative decrease in insulin levels based on need, glucose is not effectively removed from the bloodstream, resulting in abnormally high levels of blood glucose which can lead to heart disease, kidney failure, and vision loss over time. Hormones other than insulin can also lower blood glucose, including Glucagon-Like Peptide-1 (GLP-1), which is produced by cells of the intestine and is regulated by a family of proteins, called G protein-coupled receptors. A major goal of the NIH Common Fund's Illuminating the Druggable Genome program was to discover information about members of that protein family that have the potential to be developed into new therapies.[316] Research funded by the program found that one protein, called Gpr17, tends to co-occur in cells where the hormone GLP-1 is produced.[317] By investigating mouse models, the study team discovered that Gpr17 regulates GLP-1 and, therefore, has a role in regulating blood glucose. This research indicates that Gpr17 has the potential to serve as a new drug target for patients with uncontrolled type 2 diabetes.

While the discovery of new molecular targets may pave the way for future therapies, current treatment approaches are also evolving to offer more effective and lasting results. Researchers found that bariatric surgery—making physical changes to the digestive system (e.g., removing most or part of the stomach)—provided greater long-term health improvements compared to lifestyle intervention/medical management for people with type 2 diabetes.[318] To evaluate long-term efficacy, durability, and safety of bariatric surgery to treat type 2 diabetes, the NIDDK-supported Alliance of Randomized Trials of Medicine versus Metabolic Surgery in Type 2 Diabetes consortium combined data from four independent single-center randomized trials. The original studies evaluated the effectiveness of bariatric surgery compared to intensive lifestyle and medication therapy involving oral and injectable diabetes medications, including insulin, for adults with type 2 diabetes and overweight/obesity. Study participants who underwent surgery had greater improvements in blood glucose control and were more likely to achieve diabetes remission compared to participants who received a lifestyle intervention and medical management.

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[313] Mukherjee S, et al. Nat Biomed Eng. 2023 Jul;7(7):867-886. Epub 2023 Apr 27. PMID: 37106151.
[314] Lei J, et al. Sci Adv. 2022 May 13;8(19):eabm9881. Epub 2022 May 13. PMID: 35559682.
[315] Coronel MM, et al. Am J Transplant. 2023 Nov;23(11):1709-1722. Epub 2023 Aug 3. PMID: 37543091.
[316] https://commonfund.nih.gov/idg/highlights/discovering-new-target-diabetes-treatment
[317] Yan S, et al. Cell Rep. 2022 Jan 4;38(1):110179. PMID: 34986353.
[318] Courcoulas AP, et al. JAMA. 2024 Feb 27;331(8):654-664. PMID: 38411644.

As scientists refine treatments for adults with type 2 diabetes, attention is also turning to the alarming rise of the disease among children and adolescents. In FY24, NIDDK launched a nationwide consortium, called DISCOVERY of Risk Factors for Type 2 Diabetes in Youth, to address the alarming rise in youth diagnosed with type 2 diabetes over the past two decades, a trend that is expected to continue.[319] The effort aims to advance understanding of the biologic, social, and environmental drivers of youth-onset type 2 diabetes. The goal is to identify unique drivers of youth-onset type 2 diabetes that distinguish it from the disease in adults to help clinicians better understand which children are at highest risk of developing the disease and guide more effective, targeted prevention and intervention strategies. Study sites across the country are recruiting 3,600 participants, ages 9 to 14, who are considered at risk for developing type 2 diabetes.

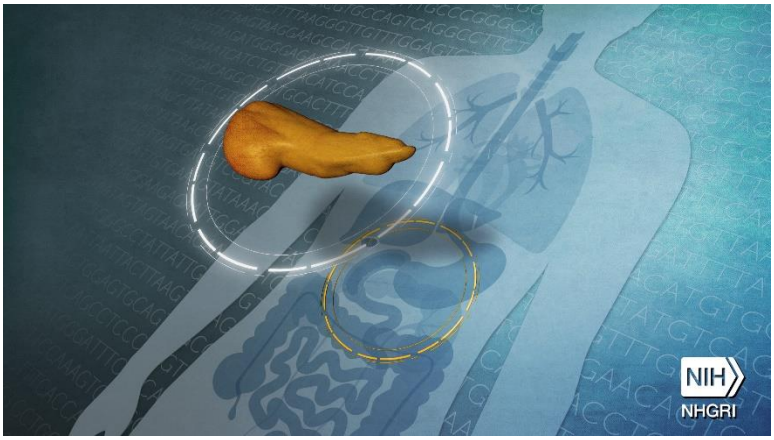


Figure 21. Beta cells in the pancreas (yellow) produce insulin. Type 2 diabetes occurs when the body cannot effectively use this insulin, or when the pancreas produces insufficient insulin to keep blood sugar levels normal. Credit: Ernesto Del Aguila III, NHGRI/NIH

Just as youth-focused efforts aim to identify risk early, other initiatives are tackling diabetes prevention in communities that face barriers to healthcare access, such as rural areas. NIDDK is supporting the Rural Alliance for Diabetes Prevention trial to help improve access and sustainability of the National Diabetes Prevention Program in underserved rural areas. [320] The National Diabetes Prevention Program is a public-private partnership that makes it easier for people at risk for type 2 diabetes to participate in an evidence-based lifestyle change program to reduce their risk. In the U.S., prevalence of type 2 diabetes is up to 17 percent higher in rural areas than in urban areas. To improve rural health care delivery, this trial will evaluate the effectiveness of the lifestyle intervention program delivered via remote platforms to residents with prediabetes in rural Kansas. Findings will help inform best practices in the delivery of the prevention program in rural communities to prevent type 2 diabetes in this high-risk population.

In addition to improving access to preventive care, researchers are also examining population-wide strategies—such as sugar-sweetened beverage taxes—that may reduce diabetes risk through policy and environmental change. NIDDK-supported findings provide evidence that these taxes may be effective to improve public health by changing consumption habits. High consumption of added dietary sugar

[319] https://discovery.bsc.gwu.edu/
[320] https://clinicaltrials.gov/study/NCT06252038

increases the risk of chronic diseases such as obesity; type 2 diabetes; and heart, kidney, and liver diseases. Despite this risk, sugar is often a main ingredient in bottled beverages such as soda, iced teas, and fruit-flavored drinks, which increase sugar consumption without providing additional nutritional value. In a cross-sectional study, researchers found that these taxes led to substantial, consistent declines in sugar-sweetened beverage purchases across five taxed cities following price increases associated with those taxes.[321] In another study of over 5 million pregnant women and their infants, taxes were associated with a significant decreased risk of gestational diabetes, as well as decreased risk of infants born small for gestational age.[322] More research will be needed in the future to understand if these benefits extend to longer-term health and the prevention of diabetes and other chronic disease in the general population.

Understanding how broader environmental exposures influence the development of type 2 diabetes is also a priority, as shown by new analyses of biospecimens from the *All of Us* Research Program. With support from NIEHS, *All of Us* began the process to analyze over 5,500 stored blood samples from participants to assess environmental exposures and their interactions with genomic and behavioral health factors. This project will generate valuable data applicable to a wide range of diseases and conditions, with a particular focus on understanding environmental influences on type 2 diabetes. Given the high prevalence of type 2 diabetes in the U.S. and its known links to environmental factors, this study aims to deepen insights into how exposures shape health outcomes.

Complementing these efforts, SI is being harnessed to uncover new insights from complex datasets that track the progression of diabetes and recovery of health over time. Launched in September 2022, the NIH Common Fund Bridge to Artificial Intelligence program is setting the stage for widespread adoption of SI that tackles complex biomedical challenges.[323] The program brings together multidisciplinary teams across four grand challenges. For example, the Salutogenesis (return to health) Grand Challenge, with support from NCCIH, is creating a flagship dataset for type 2 diabetes research.[324] This dataset, which will include data from 4,000 participants, could provide critical insights on the pathways between type 2 diabetes and a healthy state. In November 2024, the Salutogenesis project team shared preliminary results and provided access to 25 percent, or 1,067 participants-worth, of the data collected to-date.

Cross-Cutting Diabetes Research

Diabetes is a multifaceted disease that affects individuals in many ways, and researchers are working across disciplines to better understand its complexity, complications, and optimal approaches for diagnosis, treatment, and prevention. A quarter of diabetic patients suffer from diabetic foot ulcers, a life-threatening complication characterized by uncontrolled inflammation with decreased numbers of immune cells called neutrophils. Neutrophil extracellular traps are web-like structures formed by neutrophils that trap and kill pathogens, playing a crucial role in the immune response and possibly diabetic foot ulcers. NIAMS supported researchers gained new insights into the role of the immune cell response in patients with diabetic foot ulcers, and their results highlight the clinical relevance of signaling pathways regulating

[321] Kaplan S, et al. Erratum in: JAMA Health Forum. 2024 Feb 2;5(2):e240017. PMID: 38180765.
[322] Jackson KE, et al. Erratum in: Am J Prev Med. 2024 Jul;67(1):167-174. PMID: 36966893.
[323] https://commonfund.nih.gov/bridge2ai
[324] AI-READI Consortium. Nat Metab. 2024 Dec;6(12):2210-2212. PMID: 39516364.

extracellular trap formation during diabetic wound healing.[325] The findings not only correlate the clinical outcomes in patients with their molecular profile but also indicate the potential for therapeutically targeting specific signals in patients to reprogram nonhealing ulcers into those that can properly heal.

While diabetic complications like foot ulcers highlight the need for targeted therapies, other research is exploring how everyday factors, such as sleep, may influence how the body processes glucose. In a recent NHLBI- and NIDDK-funded study, adult women between 20 and 75 years old who were at risk of heart disease and diabetes were randomly assigned to 6 weeks of either 7 to 9 hours of regular sleep per night or restricted by 1.5 hours of sleep to determine how long-term limited sleep affects glucose metabolism.[326] The study found that getting just 6.2 hours of sleep per night (the median amount for people in the U.S. who do not get enough sleep) impaired insulin sensitivity; this was particularly true for post-menopausal women. These results further emphasize the importance of sleep in maintaining health.

Insights into how behavior affects metabolic health underscore the importance of acknowledging diabetes as a heterogeneous disease—one that varies widely across individuals and demands more personalized approaches. Based on the need to address the heterogeneity of diabetes, advance the goal of more precise diabetes classification, and improve precision medicine, in January 2023 the NIDDK Advisory Council approved the creation of a new Working Group to examine the understanding of heterogeneity of diabetes. The Working Group was charged with providing a detailed overview of the current state of knowledge on the heterogeneity of diabetes and of evolving concepts in this field. With this information, NIDDK would be equipped with a clear understanding of the needs and opportunities in this field that can be used to stimulate research efforts to develop more discrete definitions of subtypes of type 2 diabetes, as well as to achieve more effective prediction, prevention, and management of diabetes. The Working Group convened a workshop in June 2023 bringing together world leaders in diabetes—including academic investigators and representatives from national funding agencies and non-profit organizations—to assess existing approaches to understand disease heterogeneity and to identify research gaps, with a goal of achieving precision diabetology for all patients.[327]

To advance this vision of precision diabetology, researchers are turning to cutting-edge tools, like single-cell analysis, to uncover how genetic and cellular differences contribute to disease development and progression. Researchers from the Common Fund's Somatic Mosaicism across Human Tissues program used single-cell analysis to explore how diabetes affects insulin-producing beta cells in the pancreas, which play a crucial role in diabetes.[328] The researchers found that certain genetic factors, particularly the *HNF1A* gene, cause variations in these cells, which may contribute to the development of diabetes. By analyzing these variations at the single-cell level, the study provides valuable insights into the variability of beta cells and their role in diabetes, offering potential pathways for more targeted treatments and a better understanding of the disease.

[325] Sawaya AP, et al. EMBO Rep. 2022 Aug 3;23(8):e54558. Epub 2022 Jul 20. PMID: 35856334.
[326] Zuraikat FM, et al. Diabetes Care. 2024 Jan 1;47(1):117-125. PMID: 37955852.
[327] Cefalu WT, et al. Nat Med. 2024 Jul;30(7):1819-1822. PMID: 38992126.
[328] Weng C, et al. Nat Commun. 2023 Sep 5;14(1):5400. PMID: 37669939.

As scientific understanding of diabetes deepens at the molecular level, expert consensus is also helping to standardize care through evidence-based guidelines for screening, diagnosis, and disease monitoring. An expert committee supported by the NIH Clinical Center, in collaboration with the American Diabetes Association, developed evidence-based guidelines and recommendations for laboratory tests used to screen for, diagnose, and monitor diabetes.[329] The guidelines and recommendations were reviewed by professional organizations and opened for public comment before being finalized. Diabetes is typically diagnosed using blood glucose or Hemoglobin A1C levels, and monitored using home glucose meters, continuous interstitial glucose monitoring devices, and lab tests. The guidelines and recommendations also explore other tests, such as those for ketones, autoantibodies, and insulin, though some of these have limited current clinical value. Only tests with strong evidence or expert consensus support are recommended. These guidelines and recommendations are intended for healthcare providers, but can also inform people with diabetes, researchers, policymakers, and insurers. The goal is to support consistent, evidence-based care in managing diabetes.

Digestive Diseases

Digestive diseases span a wide spectrum of illnesses and disorders that affect the gastrointestinal tract, liver, gallbladder, and pancreas. Some digestive diseases last for a short time, while others are chronic, lasting for long periods. Together, 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, almost nine million visits to an emergency department in 2022 in the U.S. were due to diseases of the digestive system, with millions of others visiting their doctor's office for digestive system diseases.[330] 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 diagnosed, treated, and prevented.

Enhancing Diagnostic Capabilities for Digestive Diseases

Advances in diagnostics are transforming how digestive diseases are detected, understood, and managed, enabling earlier intervention and more personalized treatment strategies. The NIDDK Inflammatory Bowel Disease (IBD) Genetics Consortium[331] 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, two types of IBD that cause inflammation in the digestive tract, leading to symptoms like pain, diarrhea, and weight loss. The Consortium has aided in increasing the power of analyses to enable discovery of additional risk variants for IBD. For example, Consortium investigators identified factors that can predict whether Crohn's disease will recur after surgery to remove affected parts of the intestine, which could help healthcare providers decide on the best course of treatment to prevent disease recurrence.[332]

Building on this genetic approach to complex digestive conditions, NIDDK supported the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. The Consortium conducted studies of

[329] Sacks DB, et al. Diabetes Care. 2023 Oct 1;46(10):e151-e199. PMID: 37471273.
[330] https://www.cdc.gov/nchs/fastats/digestive-diseases.htm
[331] https://www.ibdgc.org/
[332] Hernández-Rocha C, et al. J Crohns Colitis. 2024 Apr 23;18(4):615-627. PMID: 37976264.

people with chronic pancreatitis—inflammation of the pancreas that can cause maldigestion, weight loss, nutritional deficiencies, and pain—to improve understanding of disease processes and related outcomes, such as diabetes and pancreatic cancer development. Researchers explored how immune system molecular markers can distinguish between different forms of pancreatitis and found that the markers are different between people with acute pancreatitis and people with chronic pancreatitis. These results could help improve diagnosis and lead to more tailored treatment.[333]

NIDDK and NIAID-supported researchers are developing lab models to improve diagnosis and treatment for other immune-related digestive disorders, such as celiac disease, an illness caused by an immune reaction to eating gluten—a protein found in foods containing wheat, barley or rye—that can cause symptoms such as diarrhea, fatigue, bloating, or anemia. Using intestinal cells from study volunteers, researchers developed a more accurate and personalized laboratory model of celiac disease and discovered an important role for the signaling molecule interleukin-7 in the gut's immune response to gluten.[334] This model will likely be a useful tool to test potential therapeutics before moving them forward into more complicated and expensive clinical trials. Because the method uses cells from people with celiac disease, it may eventually be possible to predict whether a certain therapy has a better chance of working in a specific individual—a step towards developing personalized medicine approaches for celiac disease.

Developing and Testing New Treatments

Innovative research supported by NIH is accelerating the development and testing of new therapies to treat digestive and liver diseases, offering hope for more effective and tailored treatments. In 2023, NIDDK launched the Clinical, Imaging, and Endoscopic Outcomes of Children Newly Diagnosed with Crohn's Disease Study.[335,336] The study aims to identify features present at the time children are diagnosed with Crohn's disease that can predict whether their disease will be healed in response to treatment. This study's 26 clinical centers, in partnership with the hundreds of children ages 6 to 17 enrolled in the study and their families, aim to develop better ways to care for children with Crohn's disease.

Beyond Crohn's disease, researchers are also working to improve outcomes for children facing acute liver failure—a life-threatening condition. Launched in 2021, and ongoing through 2024, NIDDK's Treatment for Immune Mediated Pathophysiology study is testing immunosuppressive therapy for improving survival in children with acute liver failure of unknown cause.[337] There is evidence that many of these patients have liver injury related to heightened inflammation caused by an immune response to everyday infections or environmental exposures. Treatments to reduce inflammation may improve recovery in these children, increasing their chance of surviving and avoiding a liver transplant.

Adults with chronic liver disease are also the focus of clinical research efforts, including a promising drug trial for cirrhosis supported through a collaborative NIH network. Liver cirrhosis is a chronic condition in which healthy tissue is gradually and permanently replaced with scar tissue, reducing its ability to

[333] Lee B, et al. Gastroenterology. 2023 Jul;165(1):173-186. Epub 2023 Apr 14. PMID: 37061168.
[334] Santos AJM, et al. Nature. 2024 Aug;632(8024):401-410. Epub 2024 Jul 24. PMID: 39048815.
[335] https://cameostudy.org/cameo/
[336] https://clinicaltrials.gov/study/NCT05781152
[337] https://clinicaltrials.gov/study/NCT04862221

metabolize nutrients and filter out toxins, and can lead to liver failure and death. The Liver Cirrhosis Network conducts research on liver cirrhosis resulting from various forms of chronic liver disease.[338] It is supported by NIDDK in partnership with NIAAA to address steatohepatitis caused by alcohol abuse, and with NCI to address liver cirrhosis as a major risk factor for liver cancer. In 2023, the Network launched a 2-year clinical trial to evaluate safety and efficacy of the drug rosuvastatin as a treatment for cirrhosis.[339,340]

In addition to testing pharmaceuticals, NIH is supporting pioneering research into microbial-based therapies that could redefine how inflammatory bowel diseases are treated. A team of researchers supported by the NIH Common Fund's High-Risk, High-Reward Research program broke new ground to treat gut inflammation with customized therapeutic bacteria. Normally, trillions of microbes live in our gut, helping to digest food and supporting the immune system. The researchers discovered yet another way microbes could keep our gut healthy—they could be customized to create and release therapeutic compounds directly into the gut. In studies with mice, the researchers found that feeding mice bacteria customized to create and release anti-inflammatory compounds was as effective as traditional anti-inflammatory drugs at treating ulcerative colitis.[341]

Gut-Brain Interactions in Digestive Health

The growing understanding of how the gut communicates with the brain is opening new frontiers in digestive health, with implications for nutrition, neurological disorders, and disease prevention. NIDDK-supported researchers have discovered how gut sensory cells differentiate nutritive sugars from non-caloric artificial sweeteners to guide an animal's preference for sugar. The researchers used lab-grown "mini-organs" derived from adult mice or human cells to represent the small intestine. They showed that real sugar stimulated cells to release a chemical neurotransmitter that is relayed to the brain, while artificial sweetener triggered the release of a different neurotransmitter, likely activating a different gut-brain pathway.[342] This study lays the foundation for future research to determine how other nutritional stimuli are sensed to influence food choices and raises the possibility that interventions could eventually be developed to help people reduce sugar intake.

Other studies are investigating how disruptions in gut-brain communication may signal or even contribute to the onset of chronic diseases like Parkinson's. Many people with Parkinson's disease experience gastrointestinal symptoms, which can precede diagnosis of the disease by decades and, therefore, may be one of its earliest indicators. NIDDK's Gut-Brain Communication in Parkinson's Disease Consortium is investigating the role of gastrointestinal symptoms and gut-brain communication in Parkinson's disease.[343] A goal of this consortium is to develop novel diagnostic tools and biomarkers, which could lead to ways to improve early diagnosis and prevention.

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[338] https://www.lcnstudy.org/
[339] Tapper EB, et al. Am J Gastroenterol. 2025 Mar 1;120(3):570-575. Epub 2024 Jul 17. PMID: 39018024.
[340] https://clinicaltrials.gov/study/NCT05832229
[341] Lynch JP, et al. Cell Host Microbe. 2023 Apr 12;31(4):634-649.e8. Epub 2023 Mar 31. PMID: 37003258.
[342] Buchanan KL, et al. Nat Neurosci. 2022 Feb;25(2):191-200. Epub 2022 Jan 13. PMID: 35027761.
[343] https://neurology.duke.edu/news/new-gut-brain-parkinsons-disease-consortium-studies-connection-between-gut-microbiome-and

Workshops and Meetings to Advance Digestive Disease Research

Workshops and meetings are opportunities to bring together multidisciplinary, collaborative teams and the broader research community to share ideas, identify gaps in the science, and develop strategies and plans for addressing difficult research questions and building the evidence base needed to develop new treatments and therapies. These events play a critical role in advancing research by uncovering new opportunities and sharing transformational discoveries with the scientific community and the public.

ONR, in DPCPSI within the NIH OD, and NIAID, in collaboration with several other NIH ICOs, convened an NIH-wide workshop in 2024, focused on the impact of diet on mucosal immunity (protection of the membrane that lines the intestine) and immune-mediated digestive diseases.[344] The workshop brought together NIH staff, research scientists, clinicians, people living with digestive diseases, and advocacy groups with the goals of understanding the current state of the science, identifying knowledge gaps, and discussing research opportunities that could close these knowledge gaps. Overarching topics included the impact of early exposures, including perinatal diet and maternal nutritional status, on the development and maintenance of mucosal homeostasis and gut mucosal immunity, as well as the functional interactions of these systems with the gut microbiome and subsequent development of digestive and immune-mediated diseases. Specific sessions of the workshop focused on: the impact of early dietary exposures on gut mucosal immune development; diet-derived metabolites and their functional interactions with the gut microbiome and mucosal immune system; impact of diet on intestinal homeostasis and its relationship to development of digestive diseases; regulatory immune mechanisms related to tolerance, inflammation, immunity, and neuroimmune interactions; and the role of nutrition in maintaining or altering intestinal homeostasis and immunity during health and disease states across the lifespan.

Necrotizing Enterocolitis (NEC), in which the tissue lining of the intestines becomes inflamed and dies off, is a life-threatening gastrointestinal disease that primarily affects infants born preterm (before 37 weeks of pregnancy). It is estimated that one infant in the U.S. dies almost every day from NEC. In 2024, at the request of the Secretary of HHS, NICHD convened a NEC Working Group[345] to assess the scientific evidence regarding enteral feeding practices (providing nutrition directly into the gastrointestinal tract through tubes) in premature infants and factors that may protect against or increase risk for NEC, identify important research gaps, and make recommendations for potential future research directions. The working group submitted 17 recommendations to the HHS Secretary. The three overarching recommendations were to expand research into prevention of premature birth, including ways to delay impending births beyond the window of higher NEC risk; develop a standardized definition of NEC and severity of NEC to improve epidemiologic studies and determine eligibility for trials and treatments; and ensure that research on NEC incorporates the perspectives of affected families.[346,347]

[344] https://dpcpsi.nih.gov/sites/default/files/2024-10/mucosal_immunity_workshop_executive_summary_508.pdf
[345] https://www.nichd.nih.gov/about/advisory/council/NEC-working-group-of-council
[346] https://www.nichd.nih.gov/sites/default/files/inline-files/2024.09.16_NEC_WG_report_FINAL.pdf
[347] https://www.nichd.nih.gov/newsroom/news/091924-NIH-report-necrotizing-enterocolitis

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 3.4 million Americans over the age of 40 have low vision or are legally blind.[348] 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 aged 40 and older, with another 7.3 million at risk for developing AMD.[349] 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, or around 1 in 5 adults, are estimated to have cataracts in one or both eyes. Vision loss ranks among the top causes of disability in the U.S., and as the population of older people continues to increase, the number of people experiencing vision loss is expected to increase.[350] 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.

Understanding Prevalence, Risk Factors, and Underlying Biology

Researchers are still learning what the different cells that make up the eye do and how they transmit information to the brain—foundational knowledge that is key to developing future therapies. NIAMS-funded researchers identified a pathway in the brains of mice that is activated when they see other mice scratching.[351] The researchers previously reported that the urge to scratch an itch after seeing other mice scratching is hardwired in the brain, but they have recently discovered that this "contagious itching" response operates independently of the visual cortex, the area of the brain that processes visual information. In addition to advancing knowledge of the triggers that spur itching and possibly pointing to solutions to itch-related conditions in humans, the researchers' findings suggest that some cells in the retina that were not previously linked to vision may be helpful to humans as they process and respond to visual stimuli.

Cerebral visual impairment (CVI) is a spectrum of visual impairment caused by an underlying structural or functional brain abnormality that impacts the development of visual function and processing. Because CVI is linked to brain abnormalities, often associated with conditions like cerebral palsy and cognitive delays, it is frequently underdiagnosed.[352] In 2023, as part of ongoing efforts to build awareness, promote consensus, and support research, NEI convened a workshop that was attended by clinicians, researchers, educators, therapists, people with lived experience of CVI, and caregivers. Workshop outcomes included a newly published definition of CVI that included five elements to differentiate CVI from similar conditions and improve diagnosis and understanding among clinicians.[353,354] Workshop participants also provided

[348] https://www.cdc.gov/vision-health/about-eye-disorders/vision-loss-public-health-problem.html
[349] https://www.cdc.gov/vision-health/about-eye-disorders/index.html
[350] https://www.cdc.gov/vision-health/data-research/vision-loss-facts/index.html
[351] Gao F, et al. Cell Rep. 2022 Oct 4;41(1):111444. PMID: 36198265.
[352] Gordon S, et al. Ophthalmology. 2024 Dec;131(12):1357-1358. PMID: 39572127.
[353] https://www.nei.nih.gov/events/cvi-workshop
[354] https://www.nih.gov/news-events/news-releases/nih-led-scientific-team-defines-elements-brain-based-visual-impairment-children

input regarding the development of a participant registry that could be used for research purposes and to facilitate patient recruitment into clinical studies.

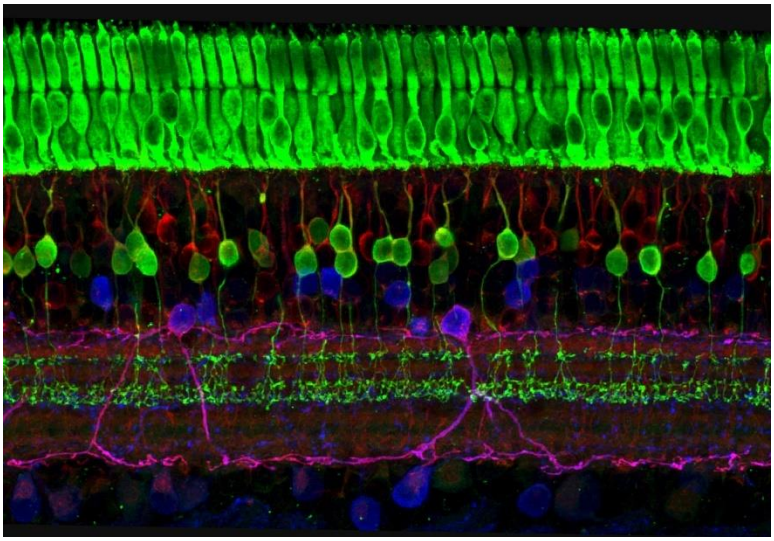


Figure 22. Image of the many layers of nerve cells in the retina. The top layer (green) is made up of cells called photoreceptors that convert light into electrical signals. The other layers support the photoreceptors and help facilitate and relay those electrical signals to the brain. Credit: Wei Li, NEI/NIH

Glaucoma is a group of eye diseases that leads to damage of the optic nerve, which transmits visual information from the eye to the brain. It causes vision loss if untreated. NEI funded a multi-cohort genome-wide association study to identify glaucoma genes in people of African ancestry, who are most frequently and severely affected by this hereditary disease. Study findings revealed previously unknown inherited genetic variants that contribute to primary open-angle glaucoma, the most common form of the disease.[355,356] Not only will these results help scientists identify new disease mechanisms and potential therapies, but it will also enable clinicians to identify individuals at increased risk who should consider aggressive early sight-saving interventions.

Using SI, NEI-supported scientists analyzed data from three, large population-based databases and identified distinct patterns of vision loss in glaucoma patients, including four advanced loss patterns and nine patterns of early loss. Glaucoma patients who identified as having African ancestry were six times more likely to have advanced vision loss archetypes compared to non-Hispanic white patients.[357] The findings underscore the importance of early glaucoma screening and detection, particularly among high-risk populations, and may inform precision medical treatment strategies to improve outcomes. Research that builds on these findings could help with identifying the specific genetic and environmental factors linked to the distinct patterns of visual field loss occurring in glaucoma patients.

[355] Cooke Bailey JN, et al. Genes (Basel). 2022 Dec 30;14(1):111. PMID: 36672852.
[356] Verma SS, et al. Cell. 2024 Jan 18;187(2):464-480.e10. PMID: 38242088.
[357]Kang JH, et al. Transl Vis Sci Technol. 2022 Jul 8;11(7):21. PMID: 35877093.

Improving Treatment and Prevention

Myopia (nearsightedness) is a significant pediatric health concern due to its rising prevalence and potential for severe complications. NIH has funded various efforts to inform treatment, including testing the efficacy of low-dose atropine, which was found to be no better than placebo at slowing myopia progression or eye elongation among children in the U.S.[358] The NEI-funded Bifocal Lenses In Nearsighted Kids studies demonstrated that multifocal contact lenses can slow the progression of myopia, and that discontinuing treatment in participants' later teenage years did not result in rebound growth.[359] Results from the studies support initiating treatment with multifocal contact lenses at younger ages and maintaining it for longer periods to obtain a greater overall benefit. Using multifocal lenses to address myopia may also reduce the likelihood of developing long-term complications like retinal detachment, glaucoma, and irreversible vision loss.

Induced pluripotent stem cells (iPSCs) are a type of stem cell that can be generated from adult cells through a process of reprogramming. Their ability to develop into nearly any cell type in the body has allowed for exciting new possibilities in biomedical research, drug development, and the treatment of various diseases, including eye diseases. In a recent NIH-supported study, researchers collected blood cells from patients with AMD, reprogrammed them into iPSCs, and coaxed them into developing into retinal pigmented epithelial cells.[360] These patient-specific retinal pigmented epithelial cells were transplanted back into the patients' eyes with the aim of restoring or improving vision. Early results from the study showed that stem cell-derived retinal cell transplantation holds great promise as a long-term solution for degenerative retinal diseases such as AMD, offering hope to patients who might otherwise lose their ability to drive, recognize faces, or read small print.

Geographic atrophy (GA) is an advanced form of AMD that can result in the progressive and irreversible loss of retinal tissue. Years of NIH-supported research led to FDA approval of Syfovre and Izervay, the first drugs for treating GA.[361] These newly available treatments are administered via injection and target different proteins within the immune system's complement pathway, which works to enhance (complement) the ability of antibodies and immune cells to clear microbes and damaged cells from the body. Clinical trials demonstrated that both drugs were well tolerated and effectively slowed the progression of GA lesions, preserving sharp central vision.[362] By slowing GA progression, these treatments may help patients retain reading ability, mobility, and independence.

Diabetic macular edema is a complication of diabetes in which high blood sugar levels damage retinal blood vessels, leading to swelling in the macula—the central part of the retina responsible for sharp, detailed vision. Diabetic macular edema is a leading cause of vision loss among people with diabetes. A recent NEI-funded clinical trial evaluated treatment strategies. It demonstrated that starting patients on bevacizumab, a less expensive medication that works by blocking growth of new blood vessels, and

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[358] Repka MX, et al. JAMA Ophthalmol. 2023 Aug 1;141(8):756-765. PMID: 37440213.
[359] Berntsen DA, et al. JAMA Ophthalmol. 2025 Feb 1;143(2):155-162. PMID: 39821272.
[360] Gupta S, et al. Stem Cells Transl Med. 2023 Aug 16;12(8):536-552. PMID: 37459045.
[361] https://www.nei.nih.gov/about/news-and-events/news/story-discovery-nei-funded-research-paves-way-new-dry-amd-drugs
[362] Khanani AM, et al. Lancet. 2023 Oct 21;402(10411):1449-1458. Epub 2023 Sep 8. PMID: 37696275.

switching to aflibercept—a more costly agent that works similarly—only if vision fails to improve adequately, results in visual outcomes comparable to initiating treatment directly with aflibercept.[363] This ”step therapy” approach was found to be a cost-saving treatment option that did not compromise long term visual outcomes. The trial is just one example of an NIH-supported effort to evaluate effective, safe, and cost-efficient treatments for sight-threatening conditions like Diabetic macular edema.

Technology Development

An NEI-funded small business conducted a clinical trial to test a novel gene therapy aimed at restoring vision in people with retinitis pigmentosa, a genetic form of blindness.[364,365] The therapy involves inserting a gene that encodes a light-detecting protein into retinal cells that do not normally respond to light. In a Phase 2 clinical trial, blind patients treated with this therapy experienced clinically meaningful improvements in vision, with no serious adverse events or off target DNA changes. Given these promising results, the small business plans to initiate a Phase 3 trial. If approved by the FDA, this therapeutic approach has the potential to restore vision for many people living with severe vision loss—including patients with macular degeneration.

The Common Fund Venture Program was launched in 2024 to support short-term research projects that can be quickly implemented in response to emerging scientific opportunities. One of the first two program initiatives, led by NEI and NIBIB, was Oculomics, focused on the development and application of novel, noninvasive eye imaging technologies, machine learning algorithms, and other tools to identify biomarkers in the eye that may offer insights into diseases affecting the entire body.[366] Oculomics can have a significant impact on early detection of diseases before the onset of symptoms, and can help clinicians with early disease intervention, risk assessment, tracking disease progression, and supportive therapeutics. Because of its noninvasive nature, Oculomics has the potential to provide advanced health care to all communities, including rural and underserved communities throughout the U.S. and world.

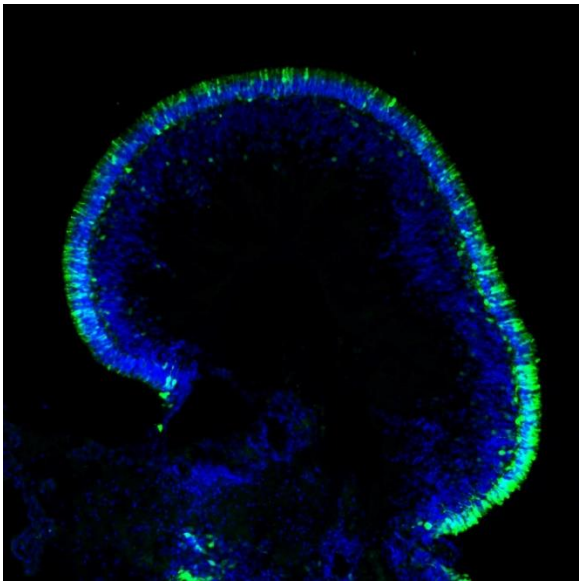
Certain cells in the body, including photoreceptor cells at the back of the retina, have small antenna-like projections called cilium that stick out from the cell membrane and are vital to their function. Mutations in the *CEP290* gene, essential for cilium formation, are the leading cause of inherited blindness occurring in the first decade of life. Blindness caused by this, and other rare gene mutations, was long considered untreatable, but recent advances in gene therapy are promising. An NEI-supported Phase 1/2 gene replacement therapy trial in adults and children with a mutation in the *CEP290* gene that causes Leber Congenital Amaurosis, showed that 11 of the 14 treated participants experienced improvements in vision and quality of life measures.[367] The tested procedure was found to be safe, with no serious adverse events or dose-limiting toxicities reported. These results pave the way for additional trails of gene replacement

[363] Jhaveri CD, et al. N Engl J Med. 2022 Aug 25;387(8):692-703. Epub 2022 Jul 14. PMID: 35833805.
[364] https://nanostherapeutics.com/2025/03/24/nanoscope-announces-publication-of-clinical-data-on-vision-restoration-in-retinitis-pigmentosa/
[365] Mohanty SK, et al. Mol Ther. 2025 May 7;33(5):2279-2290. Epub 2025 Mar 21. PMID: 40121528.
[366] https://commonfund.nih.gov/venture/oculomics
[367] Pierce EA, et al. N Engl J Med. 2024 Jun 6;390(21):1972-1984. Epub 2024 May 6. PMID: 38709228.

therapies that might demonstrate efficacy in a broad population of patients with inherited retinal disorders.

In 2023, NIH-supported scientists received the prestigious Lasker-DeBakey Clinical Medical Research Award for developing optical coherence tomography, a non-invasive imaging technique that provides detailed cross-sectional images of the back of the eye.[368] Optical coherence tomography has since transformed eye care by better revealing disease progression and response to medication, thereby enabling more informed treatment decisions, improving patient quality of life, and saving billions of dollars by reducing unnecessary procedures. New clinical applications based on this new technology are emerging, including a patient-centric home-based optical coherence tomography system developed by an NIH-funded small business, to allow physicians and patients to manage AMD in real time through remote monitoring and telemedicine.

Advances in stem cell research and tissue engineering have enabled the creation of organoids, a miniaturized and simplified version of an organ grown in the lab, that closely replicate the biology of human tissue. In 2022, the NEI funded three research teams through the 3D Retina Organoid Challenge to recreate the retina's complex cellular and neuronal circuitry in a reproducible system.[369] The Challenge required cross-disciplinary collaboration among vision researchers, engineers, and stem cell biologists to develop organoids that accurately mimic the structure and function of the retina. The resulting organoids successfully recapitulated the retina's intricate cellular and neuronal architecture, making them invaluable for advancing our understanding of eye development, modeling retinal diseases, testing new therapeutics, and exploring future applications in regenerative medicine.[370,371]



[368] https://laskerfoundation.org/winners/optical-coherence-tomography/
[369] https://www.nih.gov/news-events/news-releases/nih-solicits-next-generation-retina-organoids-prize-competition
[370] Mazerik JN, et al. Cell Med. 2018 Jun 8;10:2155179018773758. PMID: 32634188.
[371] Chen HY, et al. Elife. 2023 Mar 28;12:e83205. PMID: 36975211.

Figure 23. Image of a retinal organoid, which is lab-made retinal tissues built from patient cells. Credit: Anand Swaroop, Ph.D., NEI/NIH

Another NEI-supported research group used 3D bioprinting to study AMD, which initiates in the outer blood-retina barrier, a tissue crucial for vision. The initiation process remains poorly understood owing to the lack of physiologically relevant human models. To overcome this challenge, NEI scientists used 3D bioprinting and patient-derived stem cells to create a complex model of the eye's outer blood-retina barrier.[372] The model mimics the retinal microenvironment, and the scaffolding technique provides a theoretically unlimited supply of patient-derived tissue to study degenerative retinal diseases. New 3D bioprinted models like this one could one day speed the discovery of new cures and treatments for AMD and many other diseases and conditions.

Photobiomodulation therapy is a non-invasive treatment that uses specific wavelengths of light to stimulate cellular function, promote tissue repair, and reduce inflammation. An NEI-funded small business developed a photobiomodulation therapy for ocular diseases using its Valeda® Light Delivery System to target tissue with non-toxic low levels of light that reduce oxidative stress, inhibit inflammation, and modulate cell signaling and gene expression.[373] In a randomized safety and efficacy trial, over half of the patients experienced clinically meaningful vision improvement, as measured through the Early Treatment Diabetic Retinopathy Study chart, a widely used tool in eye examinations to measure vision clarity. No signs of phototoxicity occurred during or after treatment. For many trial participants, the gains in vision meant enhanced capacity to read, recognize faces, and perform daily tasks. The potential to use this new photobiomodulation therapy for the treatment of glaucoma and myopia is promising.

Retinopathy of prematurity is an eye condition that can occur in premature babies where abnormal blood vessels grow in the retina, leading to scarring and vision problems, including blindness. Retinopathy of prematurity disproportionately impacts rural and under-resourced communities, where residents do not typically have easy access to an ophthalmologist. In a study that included 4,244 infants from 59 sites in the U.S. and India, NEI-supported scientists found that a new SI technology that uses ocular imaging could accurately and independently detect 100 percent of severe cases.[374] Trained on tens of thousands of retinal images, this SI system has the potential to transform care in areas with limited access to specialists and prevent thousands of cases of childhood blindness. If an SI screening system is approved for widespread use, Retinopathy of prematurity would become the second eye disease for which SI can provide an independent diagnosis.

Liquid biopsy proteomics is an emerging, minimally invasive approach in ophthalmology that enables the analysis of proteins in eye fluids to gain molecular insights into eye diseases.[375] Unlike solid tissue biopsies, liquid biopsies do not harm the nonregenerative tissues of the eye and can be performed in outpatient settings. With the help of SI, NEI-supported researchers developed a way to measure ocular aging by

[372] Song MJ, et al. Nat Methods. 2023 Jan;20(1):149-161. Epub 2022 Dec 22. PMID: 36550275.
[373] https://www.prnewswire.com/news-releases/lumithera-receives-notice-of-award-for-2-5-million-national-eye-institute-grant-to-support-us-multi-center-clinical-trial-for-treating-dry-age-related-macular-degeneration-300801808.html
[374] Coyner AS, et al. JAMA Ophthalmol. 2024 Apr 1;142(4):327-335. PMID: 38451496.
[375] Wolf J, et al. J Proteome Res. 2024 Feb 2;23(2):511-522. Epub 2024 Jan 3. PMID: 38171013.

analyzing proteins in eye fluids, and they discovered that a set of just 26 proteins can accurately predict the biological "age" of an eye.[376] The newly developed technique offers potential for earlier diagnosis, personalized therapy, and deeper understanding of disease mechanisms in the human eye.

NEI-supported researchers also used SI to predict which peptides—short chains of amino acids, the molecules that make up proteins—can safely and effectively deliver drugs to eye cells. The research team specifically focused on peptides that bind to melanin, a pigment that gives color to the eye and is widely distributed throughout specialized eye structures. After training SI models on thousands of data points describing amino acid and peptide characteristics, it identified a peptide called HR97 as having the highest likelihood of safely binding to melanin in the eye and delivering drugs over several weeks. Early results showed that a drug fused with HR97 was effective for 18 days following a single injection, much longer than the three-times-a-days topical administration when the drug is given alone. The longer-lasting drug delivery made possible by this research may reduce the need for frequent treatments and offer tolerable options for treating common chronic eye diseases, including glaucoma and macular degeneration.[377]

NIH continues to provide funding to support the development of accessibility tools for people who are blind or visually impaired. For example, NEI-funded scientists recently developed the Crosswatch Smartphone app that provides real-time auditory prompts to help users identify the safest pedestrian crossing locations and stay properly aligned within crosswalks.[378] The application enables users to create 360° panoramic images, which are then transformed into overhead views and matched with Google Maps satellite imagery for accurate detection of crosswalks and precise self-localization to improve safety and usability for visually impaired pedestrians. Technological advances like this have the potential to transform the way people with disabilities, including visual impairments, navigate and experience the world.

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. More than one in seven U.S. adults suffer from kidney diseases, including chronic kidney disease, which affects an estimated 35.5 million adults.[379] 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 Therapies and Treatments

The human body is composed of approximately 37 trillion cells, and to more effectively develop treatments and cures, it is vital for researchers to understand how those cells work and interact with each other, and the world around them. To that end, the NIH Common Fund's Human BioMolecular Atlas Program brought together researchers to develop cutting-edge tools, resources, and assays to build the framework

[376] Wolf J. et al. Cell. 2023 Oct 26;186(22):4868-4884.e12. Epub 2023 Oct 19. PMID: 37863056.
[377] Hsueh HT, et al. Nat Commun. 2023 May 2;14(1):2509. PMID: 37130851.
[378] Murali VN. IEEE Int Conf Multimed Expo Workshops. 2013 Jul;2013:1-7. PMID: 25360440.
[379] https://www.cdc.gov/kidney-disease/about/index.html

necessary to construct an atlas of the human body at single-cell resolution.[380] In 2023, scientists, in conjunction with other single-cell mapping consortia, made an atlas of the human kidney, both in healthy and diseased states. They combined genetic, molecular, and cellular data into one kidney atlas, and because they had the healthy reference kidney data with which to compare, the researchers were able to find 28 different cell states that were altered in response to kidney injury. With single-cell atlases like this, scientists will be better equipped to identify possible sites of disease or injury, discover new therapies, and apply them earlier.

NIDDK's Kidney Precision Medicine Project is helping researchers understand and find new ways to treat the many distinct forms of chronic kidney disease and acute kidney injury.[381] This ambitious, multi-year project with its consortium of patient representatives, researchers, and clinicians is propelling a new era of precision medicine. Results to date have included a detailed tissue atlas of the healthy kidney, and a deep cellular and molecular analysis that revealed molecular signatures of kidney fibrosis precede the development of actual fibrosis and predict disease progression.[382,383]

The NCATS-lead National Clinical Cohort Collaborative (N3C) is a national resource of real-world data derived from electronic health records from different institutions and harmonized into data enclaves.[384] Researchers are using the N3C data enclaves to better understand a patient's journey through chronic kidney disease to inform and improve care. The data in N3C represents people across all 50 states, linked to additional datasets (such as deidentified Centers for Medicare & Medicaid Services data), and supported by collaborations across federal agencies that can be used for SI-based research to maximize patient outcomes in near-real time. In addition to an enclave focused on the renal system—the organ system that includes the kidneys, bladder, and urethra—N3C also includes enclaves focused on COVID, cancer, and one for training and education.[385,386]

Research Advances in Specific Kidney Disorders

NCATS, NIDDK, and NHLBI-supported researchers developed a new approach to better understand the biology of polycystic kidney disease (PKD), an often-life-threatening genetic disorder that affects millions worldwide. The researchers combined two ways to model the disorder—organ-in-a-dish (organoid) and organ-on-a-chip technologies—to study both the role of glucose (a type of sugar) and fluid flow (to mimic blood that constantly flows through the kidney) in forming PKD cysts.[387] The researchers showed that exposing the PKD organoid-on-a-chip model to a combination of water, sugar, amino acids (building blocks of proteins) and other nutrients caused cysts to grow relatively quickly. The cysts were absorbing glucose

[380] Lake BB, et al. Nature. 2023 Jul;619(7970):585-594. Epub 2023 Jul 19. PMID: 37468583.
[381] https://www.kpmp.org/
[382] Hansen J, et al. Sci Adv. 2022 Jun 10;8(23):eabn4965. Epub 2022 Jun 8. PMID: 35675394.
[383] Abedini A, et al. Nat Genet. 2024 Aug;56(8):1712-1724. Epub 2024 Jul 24. PMID: 39048792.
[384] https://ncats.nih.gov/research/research-activities/n3c/overview
[385] Pfaff ER, et al. Lancet Digit Health. 2022 Jul;4(7):e532-e541. Epub 2022 May 16. PMID: 35589549.
[386] https://ncats.nih.gov/research/research-activities/n3c/clinical-pilot
[387] https://ncats.nih.gov/news-events/news/2023/New-3-D-Model-Offers-Insights-into-the-Role-of-Glucose-in-a-Deadly-Kidney-Disease

and pulling in water from the fluid passing over them, making the cysts grow larger. The results could lead to better ways to test and develop treatments for PKD, and perhaps other diseases.[388]

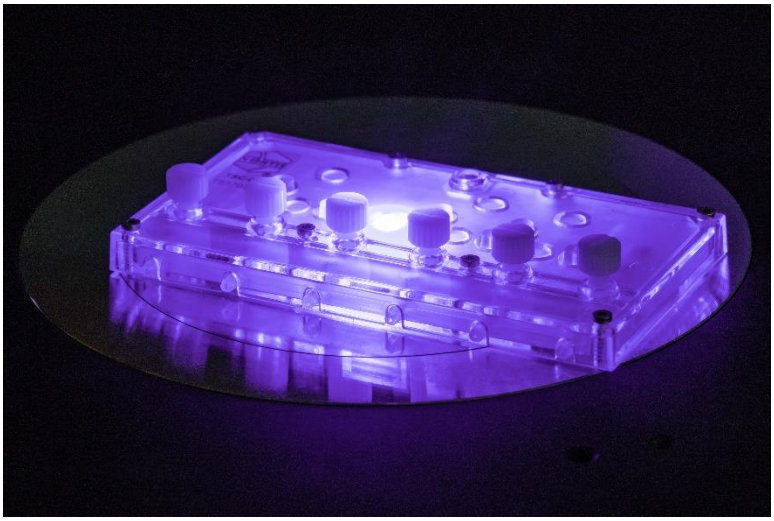


Figure 24. A kidney-on-a-chip is a small device that mimics the functions of a human kidney, allowing scientists to study kidney behavior and test drugs in a controlled, lab environment. Credit: University of Washington Photo

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, and one that often leads to life-threatening complications, including end-stage kidney disease. People with ADPKD develop fluid-filled cysts that deform and enlarge the kidneys and set off inflammation, fibrosis, and loss of kidney function. Each of these stages of kidney damage has long been regarded as irreversible, but an NIDDK-supported study showed in a mouse model of ADPKD that restoring the function of key genes can lead to dramatic shrinkage of cysts and restoration of kidney function.[389] Though there is no known way to restore the function of these genes in people with the disease, it suggests a treatment to reverse losses of kidney function in ADPKD might one day be possible.

Nephrotic syndrome is a serious condition that occurs when there is a problem with the kidney filtering system causing blood proteins to leak into the urine. NIDDK's Nephrotic Syndrome Study Network (NEPTUNE), part of the Rare Diseases Clinical Research Network, was developed to define the molecular mechanism of nephrotic syndrome for targeted therapeutic interventions.[390] NEPTUNE conducts clinical and translational research with adults and children who have these kidney diseases; or who have the rare disease Alport syndrome, which causes loss of kidney function, hearing and eye problems, and other complications. A key component of the project, NEPTUNE Match, is serving to connect people with these diseases to suitable clinical trials to find new treatments and reduce the burden of nephrotic syndrome.[391] In parallel, NEPTUNE Match empowers patients by communicating individualized reports to participants and their physicians about the molecular features of their disease state, informing decisions about the

[388] Li SR, et al. Nat Commun. 2022 Dec 23;13(1):7918. PMID: 36564419.
[389] Dong K, et al. Nat Genet. 2021 Dec;53(12):1649-1663. Epub 2021 Oct 11. PMID: 34635846.
[390] https://www.neptune-study.org/
[391] Trachtman H, et al. Kidney Int. 2024 Feb;105(2):218-230. PMID: 38245210.

suitability of available clinical trials and treatment options. This represents the first application of precision medicine in kidney function with the aim of developing targeted therapies and providing the right medication for each patient with kidney filtering diseases.

Mental Health

Mental illnesses continue to affect millions of Americans, their families, and society. More than one in five U.S. adults, or around 59.3 million people, were living with a mental illness in 2022.[392] 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 8.3 percent of all U.S. adults reporting a major depressive episode in 2021.[393] Suicide was also among the top ten leading causes of death in the U.S. in 2023.[394] Other chronic mental illnesses reducing the quality of life among Americans include schizophrenia, post-traumatic stress disorder, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, bipolar disorder, autism spectrum disorder (ASD), 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 about half of adults with mental illnesses received treatment in 2022. Mental illnesses may also be more prevalent among people who already have other chronic illnesses, such as heart disease, diabetes, cancer, and HIV.[395,396]

NIMH is the lead NIH institute for research on mental health, though several other ICOs support research in this area. Together, these ICOs support a wide range of biomedical and behavioral research focused on improving our mental health, advancing our understanding of the causes of mental illness, and developing better diagnosis, treatment, management, and prevention strategies.

Suicide Prevention

Adolescent suicide in the U.S. is a significant public health concern. Researchers supported by NIMHD and NCI analyzed national death certificate data for adolescents, aged 10 to 19, who died by suicide from 1999 to 2020 to identify trends by method of suicide, age, sex, and other demographic characteristics.[397] The study found that suicides by various means increased during this period. For example, suicides by poisoning or asphyxiation significantly increased among adolescents, and firearm suicides rose sharply among both male and female adolescents from 2007 onwards. Additionally, firearm suicide rates escalated significantly among subgroups of adolescents. The findings highlight the urgent need for effective suicide prevention strategies and provide a starting point for identifying those most in need of help.

NIMH-supported research found that 14% of adults who die by suicide visit an emergency department within the month before their death, indicating health care is a key setting for suicide prevention. In the NIMH-supported Emergency Department Safety Assessment and Follow-Up Evaluation 2 study,

[392] https://www.nimh.nih.gov/health/statistics/mental-illness
[393] https://www.nimh.nih.gov/health/statistics/major-depression
[394] https://wisqars.cdc.gov/
[395] Olfson M, et al. JAMA Psychiatry 2015;72(12):1172. PMID: 31969473.
[396] Remien RH, et al. AIDS. 2019;33(9):1411-1420. PMID: 30950883.
[397] Ormiston CK, et al. JAMA Netw Open. 2024 Mar 4;7(3):e244427. PMID: 38551558.

researchers sought to determine how a suicide prevention intervention—staff training on universal screening and collaborative safety planning—could be integrated into usual practice in eight emergency departments.[398] The intervention was found to significantly reduce suicide risk (including suicide attempts, suicide deaths, and emergency department visits) by 30 percent in the six months after patients were discharged. These results highlight the potential for emergency departments to serve as pivotal points for suicide prevention through the implementation of targeted interventions that enhance clinical care and decrease suicide risk.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a condition related to brain development that affects how people see others and socialize with them, causing problems in communication and getting along with others socially. NIMH and NICHD support research that aims to identify potential biomarkers or screening tests that help improve and expand early screening for ASD. For example, NIMH-funded researchers developed a test called the GeoPref Test, which uses eye-tracking to measure the attention toddlers give to dynamic geometric images compared to social images.[399] The test was given to over 1,800 toddlers aged 12 to 48 months and results showed that those with ASD paid more attention to geometric images. In a separate effort, NIMH-supported scientists evaluated whether a multistage ASD screening protocol could improve ASD detection in early intervention settings, finding that it led to a noticeable increase in ASD diagnoses, especially among Spanish-speaking families.[400] Researchers supported through a collaboration between NIMH and NICHD also used electronic health records to develop a predictive model to identify infants who might later receive an ASD diagnosis.[401] By continuing to support and expand these research efforts, NIH will enhance the lives of many children and their families through timely and effective ASD interventions.

NIH-funded scientists used MRI scans to track brain growth in infants to learn how ASD and fragile X syndrome—a genetic disorder that causes intellectual disabilities, behavioral problems and physical abnormalities—develop.[402] They found that babies who later developed ASD had normal-sized amygdalae (the brain's emotion-processing center) at six months, but these grew unusually fast between 6 and 24 months, becoming noticeably larger at one year of age. This rapid amygdala growth was linked to more severe social challenges at age two. In contrast, infants with fragile X syndrome had an enlarged caudate region (part of the brain involved in learning and regulating behavior) from as early as six months, which was tied to more repetitive behaviors. The study shows that brain changes in ASD and fragile X syndrome happen on different timelines and affect different parts of the brain, which may help guide earlier and more specific interventions.

ASD poses significant challenges for affected individuals and their caregivers. ORIP, in DPCPSI within the NIH OD, supports NIH research by providing essential animal models, facilities, training, and resources to scientists. In collaboration with the ORIP-supported California National Primate Research Center,

[398] Boudreaux ED, et al. Contemp Clin Trials. 2020 Aug;95:106075. Epub 2020 Jun 19. PMID: 32565041.
[399] Wen TH, et al. Sci Rep. 2022 Mar 11;12(1):4253. PMID: 35277549.
[400] Sheldrick RC, et al. JAMA Pediatr. 2022 Mar 1;176(3):262-269. PMID: 34982099.
[401] Engelhard MM, et al. JAMA Netw Open. 2023 Feb 1;6(2):e2254303. PMID: 36729455.
[402] Shen MD, et al. Am J Psychiatry. 2022 Aug;179(8):562-572. Epub 2022 Mar 25. PMID: 35331012.

researchers studied large groups of nonhuman primates in naturalistic settings and discovered that those with low behavioral sociability also had low levels of the hormone vasopressin.[403] The findings point to the potential for using vasopressin levels as a biomarker for early ASD detection and intervention.

Mental Health Prevention and Treatment

Low-income homebound older adults often lack access to mental health treatments due to their inability to leave home and a shortage of geriatric mental health professionals. An NIMHD-supported study evaluated the cost-effectiveness of counselor-delivered video-conferenced behavioral activation (Tele-BA) compared to clinician-delivered problem-solving therapy (Tele-PST) and telephone support calls.[404] The analysis used data from a trial with 277 participants, measuring costs and quality-adjusted life-years to determine cost-effectiveness. Both Tele-BA and Tele-PST were found to be cost saving compared to telephone support calls. While Tele-BA was not as cost-effective as Tele-PST, it remains a valuable option for addressing the geriatric mental health workforce shortage and improving access to depression care for homebound older adults. The research highlights the potential for telemedicine to address mental health differences in underserved, homebound populations by providing affordable and accessible care.

The Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Program, funded by NIMH, continues to support mental health services for severe psychiatric disorders through innovative, multidisciplinary research. It focuses on practice-based studies with near-term impact, incorporating input from service users, families, clinicians, and administrators for relevant and quick application.[405,406] Since its inception, the program has supported 15 research centers across the U.S., addressing varied populations and settings, and covering areas from intervention optimization to implementation research. Many centers use digital health platforms and data science to improve diagnosis, monitor illnesses, and deliver mobile health interventions. Insights from the program offer promise to significant advancements in mental health research and provide valuable resources for the broader scientific and practice communities.

In 2023, FDA approved zuranolone, a new medication to treat postpartum depression, which affects about 1 in 9 new mothers.[407] Unlike its predecessor brexanolone, which requires an intravenous infusion in a hospital, zuranolone can be taken as an oral pill, making it easier to use and more accessible.[408] Both medications work quickly to reduce depressive symptoms by targeting the same biological mechanism, a discovery made through extensive research funded by NIH. Zuranolone increases accessibility to treatment for postpartum depression and may inform the development of treatments for other types of depression.

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[403] Parker KJ. Mol Psychiatry. 2022 Jun;27(6):2650-2658. Epub 2022 Apr 1. PMID: 35365807.
[404] Chen GJ, et al. BMC Psychiatry. 2022 Oct 17;22(1):648. PMID: 36253766.
[405] 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
[406] https://grants.nih.gov/grants/guide/pa-files/PAR-24-210.html
[407] https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-treatment-postpartum-depression
[408] Deligiannidis KM, et al. Am J Psychiatry. 2023 Sep 1;180(9):668-675. Epub 2023 Jul 26. Erratum in: Am J Psychiatry. 2025 Mar 1;182(3):311. PMID: 37491938.

Years of NIMH-supported research led to the discovery that ketamine—a drug approved by the FDA in 1970 as an anesthetic—has a robust, rapid therapeutic effect on treatment-resistant depression when administered intravenously. The research led to the development and FDA approval in 2019 of the ketamine derivative, esketamine.[409] Esketamine is the first and only monotherapy to treat adults with treatment-resistant depression, and it can be administered more easily as a nasal spray.[410] NIMH supports additional research on the ability of ketamine and its derivatives to treat depression. For example, researchers recently found that administration of a brief cognitive training program after a single ketamine infusion could extend the antidepressant effects of ketamine over at least 30 days.[411] These findings demonstrate the benefit of ketamine in treating depression, and of repurposing existing FDA-approved drugs for other purposes.

Effective treatments for mental illnesses exist, but finding the right treatment for each individual often involves a lengthy trial-and-error process. To address this challenge, NIMH launched a new initiative called the Precision Psychiatry Initiative: Innovation Funnel and Individually Measured Phenotypes to Advance Computational Translation.[412] This initiative aims to encourage and support research that uses behavioral measures and computational methods to define novel clinical signatures.[413] These signatures can be used for individual-level prediction and clinical decision-making in mental disorders. The overall goal of the newly launched initiative is to improve the precision and effectiveness of mental health treatments, reducing delays and enhancing personalized care.

In 2023, the U.S. Surgeon General issued an Advisory that calls attention to the growing concerns about the effects of social media on youth mental health.[414] Recognizing these risks, NIMH is supporting research that aims to understand the bidirectional relationships between social media use and adolescent mental health, including psychiatric symptoms, resilience, and risk for psychopathology.[415] By identifying and analyzing risk and protective factors associated with technology and digital media use, researchers, policymakers, and practitioners can develop targeted strategies that mitigate its potential harms while maximizing benefits.

Resources Supporting Collaboration and Innovation

The Early Psychosis Intervention Network is a NIMH-supported initiative aimed at enhancing coordinated specialty care to improve early identification, diagnosis, clinical assessment, intervention effectiveness,

[409] https://www.nimh.nih.gov/news/science-updates/2023/cracking-the-ketamine-code
[410] https://www.pharmacytimes.com/view/esketamine-receives-fda-approval-for-adults-with-treatment-resistant-depression
[411] Price RB, et al. Am J Psychiatry. 2022 Dec 1;179(12):959-968. Epub 2022 Sep 21. PMID: 36128684.
[412] https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/individually-measured-phenotypes-to-advance-computational-translation-in-mental-health-impact-mh
[413] https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-25-195.html; https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-23-106.html; https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-25-190.html
[414] https://www.hhs.gov/sites/default/files/sg-youth-mental-health-social-media-advisory.pdf
[415] https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-23-115.html; https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-23-116.html; https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-24-181.html; https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-24-180.html

service delivery, and health outcomes for early psychosis.[416] To foster knowledge sharing and promote accessible early psychosis care resources, the Network Data Coordinating Center launched a web portal to make the Web-based Core Assessment Battery available to all early psychosis care clinicians. It will help them assess key domains of early psychosis, recovery, and treatment, and serve as a basis for common data collection across all Network clinics. As of September 2024, the Network supported eight regional scientific hubs, enrolling approximately 4,000 participants from more than 100 clinics across 17 states. Coordination of activities by the Network helps ensure consistent and effective data collection and treatment across all participating clinics.

The Accelerating Medicines Partnership Schizophrenia Initiative is a collaborative effort to study schizophrenia involving NIMH, FDA, European Medicines Agency, and multiple public and private organizations.[417] About 2,000 individuals at high risk for psychosis and 640 healthy controls were recruited to provide extensive data, including clinical assessments, brain scans, blood samples, and smartphone data.[418] This information will be analyzed and used to develop new tools and treatments aimed at preventing or better managing schizophrenia. Additionally, the data will be made available to the broader research community through the NIMH Data Archive. The global reach of the Initiative and its harmonized, innovative methods offer potential for driving the development of new treatments that address critical unmet clinical and public health needs in individuals at high risk for psychosis.

In 2023, the *All of Us* Research Program partnered with NIMH to expand research on cognitive function and mental well-being. Two new surveys were launched through this collaborative effort to learn more about a broad spectrum of behavioral and emotional health topics like depression, anxiety, self-harm, and other related issues.[419] Over 500,000 participants in the *All of Us* program were eligible to take these surveys in English or Spanish. Researchers will use data collected through the surveys to better understand the relationships between cognitive performance, health factors, and behavior affecting mental health. Integrating the newly collected information with other *All of Us* data sources will facilitate a better understanding of mental health conditions and lead to better treatments.

Researchers supported by the NIMH-funded PsychENCODE Consortium produced the largest and most advanced multidimensional maps of gene regulation networks in the brains of people with and without mental disorders.[420] These maps provide insight into how genetic risks contribute to mental disorders like schizophrenia, post-traumatic stress disorder, and depression. In 2024, the research was published across several papers in scientific journals.[421] The publications describe how different genes are regulated in brain regions involved in crucial functions like memory and emotion; and they highlight new methods and tools for data analysis, including a web-based platform, known as PsychSCREEN, that offers interactive

[416] https://www.nimh.nih.gov/research/research-funded-by-nimh/research-initiatives/early-psychosis-intervention-network-epinet
[417] https://www.ampscz.org/
[418] Wannan CMJ, et al. Schizophr Bull. 2024 Apr 30;50(3):496-512. PMID: 38451304.
[419] https://allofus.nih.gov/article/announcement-all-us-research-program-starts-collecting-new-mental-health-and-well-being-data
[420] https://www.nimh.nih.gov/news/science-updates/2024/scientists-map-networks-regulating-gene-function-in-the-human-brain
[421] https://www.science.org/collections/psychencode2

visualization data from a range of brain cell types.[422] The PsychENCODE data, accessible through the NIMH Data Archive, will help researchers pinpoint genetic variants that are likely to play a causal role in mental illnesses and identify potential molecular targets for new therapeutics.

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, roughly one in four adults over age 18 have arthritis, the swelling and tenderness of one or more joints; and around 18.8 percent of women over age 50 have osteoporosis, a skeletal disorder characterized by low bone mass, in the neck or spine. Musculoskeletal and skin diseases often occur as complications from other conditions, compounding the impact on a person's quality of life and health. NIH-supported investigators continued to confront the widespread burden of these disorders, guided by NIAMS. Researchers are working to advance the full discovery-to-delivery continuum—spanning molecular insights, tool development, and first-in-human therapeutics—while emphasizing cost-effective, patient-accessible solutions.

Advancing Muscle Biology Research

Myotonic dystrophy is an inherited multisystem condition that mainly causes progressive muscle loss, weakness, and prolonged muscle contractions (myotonia). In FY22, NIH Clinical Center rehabilitation scientists partnered with scientists from NINDS to create a low-cost HandClench Relaxometer that can more accurately quantify grip-induced myotonia in myotonic dystrophy patients.[423] A clinical study in individuals with myotonic dystrophy type 1 and age-matched healthy controls validated the device design and demonstrated its repeatability, reliability, and sensitivity in assessing myotonia and strength in these individuals. These findings suggest the HandClench Relaxometer could be a patient-friendly tool for longitudinal tracking of grip myotonia and for use as a biomarker in investigational therapy trials across a range of clinical sites.

Mitochondrial diseases are a group of inherited conditions that affect 1 in 5,000 people and have very few treatments. Now, for the first time, scientists can map mutations that cause often devastating mitochondrial diseases. NIEHS investigators solved the first 3D, high-resolution structures of the human protein Twinkle helicase variant W315L, revealing assemblies critical for mitochondrial DNA replication.[424] The 3D models allowed the scientists to map numerous disease-causing mutations onto functional surfaces of the protein to better understand how these mutation variants perturb DNA binding and translocation. This work brings scientists closer towards the development of targeted treatments for patients who have mitochondrial diseases, such as a muscle function disorder that leads to the loss of eye movement, a rare genetic disorder that can cause hearing loss, and various other hereditary disorders in newborns and young children.

Duchenne Muscular Dystrophy (DMD) is a rare form of muscular dystrophy primarily affecting young boys. The disease is caused by the loss of dystrophin protein in muscle tissues, leading to progressive muscle

[422] https://psychscreen.wenglab.org/psychscreen
[423] Bulea TC, et al. Neuromuscul Disord 2022;32(4):321-331. PMID: 35305880.
[424] Riccio AA, et al. Proc Natl Acad Sci U S A 2022;119(32):e2207459119. PMID: 35914129.

weakness and difficulties with walking, balance, and daily activities. DMD patients' lives are drastically shortened by cardiomyopathy and respiratory complications. Supported by an NINDS small-business grant, and in partnership with NCATS, a small biopharma company advanced the novel steroidal anti-inflammatory vamorolone from discovery to pivotal clinical trials and, ultimately, FDA approval for DMD.[425,426] Vamorolone offers the benefits of corticosteroids, such as improving muscle strength, but with fewer negative side effects, making it a safer option for patients. A 24-week randomized trial in 121 boys showed that vamorolone improved time-to-stand velocity and other motor end points while avoiding growth stunting and bone morbidities.[427] These results demonstrate how early NIH investment can de-risk therapies and deliver the first-in-class steroid alternative for DMD.

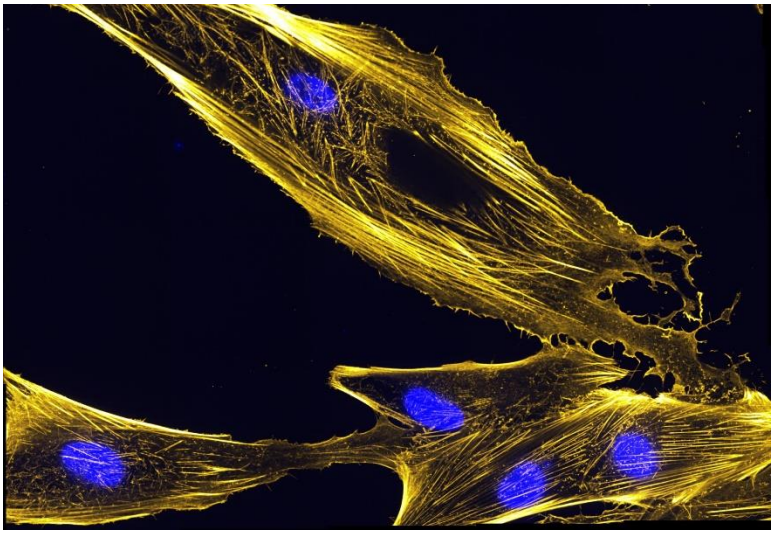


Figure 25. Immunofluorescence image of actin bundles in muscle precursor cells called myoblasts. The actin is labeled with a yellow fluorescently-tagged molecule. Cell nuclei are shown in blue. Credit: Alex Ritter, Jennifer Lippincott Schwartz and Gillian Griffiths, NIH

Advancing Bone and Cartilage Biology Research

Nested within the 25,871-participant Vitamin D and Omega-3 Trial, a NIAMS-supported ancillary analysis evaluated whether daily vitamin D_3 and marine omega-3 fatty acids (found in fish oil supplements) improve bone outcomes or prevent autoimmune disease in generally healthy adults. After 5.3 years, vitamin D_3 neither reduced total fractures nor protected specific sites such as hip or wrist, challenging decades of bone-health supplementation advice.[428] In contrast, participants receiving vitamin D_3—with or without fish oil—experienced a 22 percent to 30 percent lower incidence of physician-confirmed autoimmune disorders, including rheumatoid arthritis and psoriasis.[429] Because nearly one-third of U.S. adults aged 60 and over routinely take vitamin D, these divergent results separate skeletal and immunologic effects and

[425] https://www.ninds.nih.gov/news-events/news/highlights-announcements/ninds-small-business-funding-leads-new-therapy-duchenne-muscular-dystrophy
[426] https://ncats.nih.gov/news-events/news/fda-approval-for-duchenne-muscular-dystrophy
[427] Guglieri M, et al. JAMA Neurol 2022;79(10):1005-1014. PMID: 36036925.
[428] LeBoff MS, et al. N Engl J Med 2022;387(4):299-309. PMID: 35939577.
[429] Hahn J, et al. BMJ 2022;376:e066452. PMID: 35082139.

support targeted supplementation aimed at reducing autoimmune risk rather than blanket fracture prevention.

Sparked by a 2002 NIAMS call for tools that could precisely gauge bone strength, a public-private consortium with the Foundation for NIH and the American Society for Bone and Mineral Research set out to modernize osteoporosis drug evaluation. The group's Study to Advance Bone Mineral Density as a Regulatory Endpoint merged individual-patient data from more than 50 trials and showed that a two-year gain in total-hip bone mineral density predicts most of the fracture reduction achieved by approved therapies.[430] Equipped with these data, the FDA in 2022 approved bone mineral density measured by dual-energy x-ray absorptiometry as a primary endpoint for Phase 3 osteoporosis trials.[431] In addition to laying the groundwork for much needed patient therapies, the study investigators have created a rich dataset that holds promise for informing future studies in osteoporosis.

Obesity can increase a person's risk of bone fragility, even when they have a healthy amount of bone mass. This fragility stems from poor bone quality, potentially caused by deficiencies in bone structure. In mechanistic mouse studies, NIAMS-funded scientists linked diet-induced obesity to weakened bones through a well-known signaling pathway in osteocytes (bone cells). Mice fed a high-fat or high-carbohydrate diet developed brittle femurs despite normal bone mass and an analysis of gene expression pinpointed overactive signaling of a small protein, transforming growth factor beta, in osteocytes as key.[432] Genetic or pharmacologic dampening of the signaling molecule restored collagen quality and bending strength. Their findings suggest that osteocytes are key in controlling bone quality in response to high-fat and high-carbohydrate diet and reframes skeletal complications of obesity and diabetes as signaling problems that are potentially treatable with medication, not merely weight-related.

Although recombinant bone morphogenetic protein 2, a small signaling protein, is an FDA-approved therapeutic for fracture healing, its use has been limited by several adverse side effects that result from the high doses needed to generate sufficient bone to fill large gaps. To make the protein safer and more cost-effective, NIAMS-supported engineers created a chemically modified mRNA encoding the protein and loaded it into a biodegradable scaffold to promote bone repair. In rats bearing critical femoral gaps, a single low dose of the mRNA-protein scaffold achieved 100 percent bridging at doses 100-fold lower than commercial recombinant protein and prevented the formation of bone in unwanted places.[433] Parallel work wrapped bone morphogenetic protein 2 in a thin membrane, which further confined new bone to the injury site and enabled spatially controlled bone regeneration.[434] Both strategies underscore that precise spatial and temporal delivery, rather than higher drug concentration, drives effective bone formation and lays a path toward first-in-human trials aimed at challenging fractures that now resist standard care.

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[430] Vasikaran SD, et al. J Bone Miner Res 2024;in press. PMID: 38677307.
[431] https://fnih.org/news/fda-approves-biomarker-qualification-plan-for-the-first-surrogate-endpoint-in-anti-osteoporosis-drug-trials/
[432] Dole NS, et al. JCI Insight 2024;9(16):e167501. PMID: 39171528.
[433] Krishnan L, et al. Sci Adv 2022;8(9):eabl6242. PMID: 35171668.
[434] Priddy LB, et al. J Orthop Res 2023;41(1):130-140. PMID: 35340049.

Tiny molecular "gates" known as voltage-gated sodium channels are found on surfaces of cells such as neurons. They work to create small electric currents, which is how our nerves send signals throughout the body. Osteoarthritis (OA) is the most common joint disease, but currently, there are no effective methods that simultaneously prevent joint degeneration and reduce pain. To investigate whether these channels play a role in OA, NIAMS-supported researchers studied voltage-gated sodium channels in cartilage and found that a specific channel, Nav1.7, was active in the cartilage cells of joints with OA. When researchers blocked this channel in a mouse model, it helped restore normal cell function, relieved pain, and preserved joint structure without harming nerve function elsewhere.[435] Because drugs that block Nav1.7 (such as carbamazepine) are already FDA-approved for neural pain, these findings suggest they could potentially be repurposed to treat OA in humans.

The 2023 FDA approval of delandistrogene moxeparvovec—the first gene therapy for DMD—crowns decades of NIAMS-backed discovery science. Early NIAMS-supported research decoded the dystrophin gene and pioneered adeno-associated virus vectors that deliver functional micro-dystrophin to muscle fibers.[436] In this pivotal clinical trial, treated boys produced new dystrophin and gained clinically meaningful improvement of their motor skills. Approval offers families a transformational option for treating DMD and has the potential to advance gene-replacement strategies for other severe diseases that affect skeletal muscles.

Given sufficient time, fractured bones can heal with the help of immune cells, stem cells, and a variety of proteins. Investigators at NIDCR discovered that a protein called biglycan, which helps form the structural scaffolding outside of cells, plays a key role in bone growth and repair. Mice lacking biglycan had bones with a weaker outer layer, smaller calluses (the new bone that forms during healing), and were mechanically weaker overall. This was because the specialized bone-forming cells (osteoblasts) could not mature properly, and the body's natural inflammatory signs that promote healing were weaker.[437] Restoring biglycan expression in mice corrected these issues, highlighting it as a potential target for new treatments. These insights improve our understanding of how the body builds bone and suggests that focusing on biglycan could help accelerate bone healing and even combat osteoporosis.

Advancing Skin Biology Research

NIAMS-supported researchers leveraged 3D bioprinting to fuse six primary human cell types into a multilayer construct that recreates the three layers of skin—epidermis, dermis, and hypodermis. When tested outside the body, the printed skin maintained native-like architecture and matured properly. When grafted onto wounds in mice, the construct integrated with surrounding tissue, stimulated the formation of new blood vessels, and accelerated wound closure.[438] This work has potential as an off-the-shelf graft that could shorten recovery times for burns, trauma, and battlefield injuries while reducing reliance on donor tissue.

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[435] Fu W, et al. Nature 2024;625(7995):557-565. PMID: 38172636.
[436] Mullard A. Nat Rev Drug Discov 2023;22: e74-e75. PMID: 37353665.
[437] Shainer R, et al. Front Physiol 2023;14:1119368. PMID: 36875017.
[438] Jorgensen AM, et al. Sci Transl Med 2023;15(716):eadf7547. PMID: 37792956.

Acne involves excess production of lipids, particularly squalene, increased growth of the bacteria *Cutibacterium acnes*, and heightened inflammatory responses. NIAMS-funded scientists mapped early human acne lesions to reveal how altered lipids ignite inflammation. The researchers found that squalene-rich hair follicles contain macrophages expressing a receptor called TREM2 (Triggering Receptor Expressed on Myeloid Cells 2). These macrophages activate pro-inflammatory pathways while simultaneously disabling antibacterial defenses, preventing the immune system from clearing *Cutibacterium acnes* and prolonging lesion development. By identifying TREM2 and lipid metabolism as upstream drivers of acne, the study points to new molecular targets for non-antibiotic, macrophage-directed acne treatments.[439] Translating these insights could markedly improve care for the one in ten people worldwide affected by chronic acne.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and often debilitating condition that affects many body systems. It 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. It is estimated that up to 3.3 million Americans have ME/CFS, and that most of them—over 9 in 10—have not been diagnosed by a doctor.[440] NIH is invested in discovering the basic mechanisms associated with ME/CFS, identifying treatments, and supporting research that will improve the lives of people with ME/CFS.

In 2016, NIH launched the NIH Intramural Study on ME/CFS,[441] which took place at the NIH Clinical Center, focused on individuals who developed ME/CFS after an infection, known as post-infectious ME/CFS. The goal was to closely examine the clinical and biological characteristics of the disease to improve our understanding of its causes and progression. The study was led by NINDS in collaboration with NIMH, NHLBI, NIEHS, and NIAID. Researchers used strict criteria to select participants and matched controls for deep phenotyping. One key finding, published in 2023, was the changes in brain and immune function that disrupt how feelings of fatigue are processed in people with ME/CFS. The paper also revealed sex-based differences in gene expression profiles in muscle, immune cell populations, and metabolic markers.[442] Another group of researchers found that high levels of the WASF3 protein disrupt mitochondrial function and energy production in muscle cells, leading to fatigue. Lowering WASF3 levels improved mitochondrial function.[443] These findings provide unique insight into the underlying pathophysiology of ME/CFS and suggest a potential treatment path for ME/CFS and other fatigue-related conditions.

A few years after the aforementioned NIH Intramural Study on ME/CFS began, the COVID-19 pandemic hit and researchers and doctors noticed that some people who get COVID-19 do not quickly recover, but continue to have symptoms, such as extreme tiredness, especially after activity; problems with memory,

[439] Do TH, et al. Sci Immunol 2022;7(73):eabo2787. PMID: 35867799.
[440] https://www.cdc.gov/me-cfs/about/index.html
[441] https://clinicalstudies.info.nih.gov/protocoldetails.aspx?id=16-N-0058
[442] Wang, P. Y., et al. Proc Natl Acad Sci U S A. 2023 Aug 22;120(34):e2302738120. Epub 2023 Aug 14. PMID: 37579159.
[443] Walitt, B., et al. Nature communications, 15(1), 2024 Feb 21;15(1):907. PMID: 38383456.

often called brain fog; and a feeling of being lightheaded or dizzy. This condition became known as post-acute sequelae of SARS-CoV-2 infection, better known as long COVID; and it shares many of the same symptoms as post-infectious ME/CFS.[444] Researchers at the NIH Clinical Center studied 12 patients with long COVID with ongoing issues like cognitive difficulties and fatigue, comparing their results to healthy people. This observational study found broad immune dysregulation in the central nervous system; and helps advance our understanding of this new condition, in addition to beginning to bridge the knowledge gap between post-infectious ME/CFS and long COVID.[445]

Following the publication of these groundbreaking studies, NINDS hosted a symposium in May 2024 to share the findings with a broader audience. The symposium fostered a collaborative environment among researchers, clinicians, and patient advocates, promoting dialogue around current findings and future directions in ME/CFS research.

Building on previous ME/CFS research and to advance the field further to better understanding and treatment, in 2024 an NINDS-lead working group of scientists created an ME/CFS Research Roadmap.[446,447] The roadmap sets eight priority research areas: chronic infections, immune system, nervous system, cardiovascular circulation, metabolism, physiology, less-studied pathologies, and genomics/genetic susceptibility. To ensure the research benefits those most in need—patients and their families—there is an emphasis on input from those with lived experience with ME/CFS. The roadmap calls for collaboration among stakeholders to drive the field towards clinical trials, with the NIH-wide ME/CFS Working Group set to review and implement the roadmap's recommendations. With this roadmap, NIH is laying a foundation to better understand, diagnose, and treat ME/CFS and related conditions.

Obesity

Obesity is a serious, common, and costly chronic disease affecting more than two in five adults and one in five children and adolescents in the U.S.[448] 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. Annual obesity-related medical care costs in the U.S. were estimated to be nearly $173 billion in 2019 dollars.[449] 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 develop obesity, how to prevent and treat obesity, and how to unlock the basic biological activities underlying obesity and its numerous complications.

Prevention and Risk Factors

[444] https://www.cdc.gov/long-covid/about/index.html
[445] Mina, Y., et al. Neurol Neuroimmunol Neuroinflamm. 2023 May 5;10(4):e200097. PMID: 37147136.
[446] https://www.ninds.nih.gov/about-ninds/who-we-are/advisory-council/nandsc-mecfs-research-roadmap-working-group
[447] https://www.ninds.nih.gov/news-events/directors-messages/all-directors-messages/advancing-research-mecfs
[448] https://www.cdc.gov/obesity/index.html
[449] https://www.cdc.gov/obesity/basics/consequences.html

Preventing obesity and its related health consequences requires a deeper understanding of the biological, behavioral, environmental (including the food, built, and social environments), and generational risk factors that contribute to disease development across the lifespan. In a study supported by NIDDK, researchers found that a responsive parenting intervention shown to help new parents reduce risk for overeating and overweight in their firstborn children also had beneficial spillover effects on the growth of their second born children years later. The study, called SIBSIGHT, followed an earlier NIDDK-funded clinical trial—Intervention Nurses Start Infants Growing on Healthy Trajectories—in which nurses delivered information in the homes to first-time parents, including education on infant feeding, sleep, and play.[450,451] The findings provide hope that a parenting strategy taught once could help with setting children and their future siblings on a healthy growth trajectory.

While behavioral interventions in early life can lay the groundwork for healthier outcomes, family history also plays a critical role in determining long-term risk. In 2023, a study funded by NHLBI demonstrated that parental history of obesity and smoking were associated with a higher risk of future cardiovascular disease in offspring.[452] However, some of the other parental modifiable risk factors (such as parental history of hypertension, diabetes, and high cholesterol) were not associated with offspring cardiovascular disease risk. These findings suggest that in addition to parental cardiovascular disease, the presence of parental obesity should prompt a focus on disease prevention in offspring.

In addition to familial and behavioral influences, research is uncovering how genetic predispositions further shape the development and severity of obesity-related diseases. Studies supported by NIDDK through its Nonalcoholic Steatohepatitis Clinical Research Network in children and adults with nonalcoholic fatty liver disease (also known as metabolic dysfunction-associated steatotic liver disease) have linked genetic risk factors and outcomes to disease stage, with severe, later-stage disease associated with a higher risk of complications and death.[453,454] These findings can inform clinical care for this disease, which is increasingly common in the U.S. and around the globe.

Treatments and Clinical Guidelines for Patients with Obesity

A growing body of research is shaping how obesity and its related conditions are treated, with new strategies ranging from lifestyle interventions to cutting-edge therapeutic discoveries that inform clinical guidelines and long-term care. Over the last decade, NIAMS-funded clinical trials have measured the efficacy of weight loss through intensive diet and exercise interventions for the management of knee osteoarthritis.[455] The research suggests that weight loss achieved through these interventions represents an effective non-drug treatment for older adults with knee osteoarthritis. These findings are reflected in

[450] Savage JS, et al. Obesity (Silver Spring). 2022 Jan;30(1):183-190. Erratum in: Obesity (Silver Spring). 2022 Apr;30(4):954. PMID: 34932886.
[451] https://www.nih.gov/news-events/news-releases/parenting-program-prevent-obesity-firstborn-children-benefits-siblings
[452] Taylor CN, et al. J Am Heart Assoc. 2023 Mar 21;12(6):e027881. Epub 2023 Mar 9. PMID: 36892090.
[453] Goyal NP, et al. Hepatology. 2023 Jan 1;77(1):197-212. Epub 2022 Jun 20. PMID: 35560106.
[454] Sanyal AJ, et al. N Engl J Med. 2021 Oct 21;385(17):1559-1569. PMID: 34670043.
[455] Lim YZ, et al. Osteoarthr Cartil Open. 2022 Aug 5;4(4):100298. PMID: 36474793.

recent updates to clinical practice guidelines, which strongly advocate for weight loss and exercise in patients with osteoarthritis who have obesity.

While structured weight loss remains a cornerstone of treatment for many obesity-related conditions, researchers are also exploring innovative approaches to dietary timing that offer promising metabolic benefits. In an NIDDK-funded study to improve the health of people who do shift work—which can disrupt cycles of sleeping and eating and is associated with metabolic disease—researchers found that time-restricted eating was feasible for firefighters on 24-hour schedules and led to cardiometabolic benefits, particularly for those who had health risks at the start of the study.[456] A group of study participants followed a time-restricted eating intervention, which limited calorie intake to 10 hours/day. Compared to a standard of care group, participants following a time-restricted eating strategy had improved blood sugar, blood pressure, and cholesterol by the end of the study. In another NIDDK-supported study to evaluate weight-loss interventions, researchers found that time-restricted eating was effective for weight loss and lowering blood sugar levels compared to daily calorie counting in adults with type 2 diabetes and obesity.[457] The encouraging results show health benefits of meal timing across different groups of people.

The challenge of maintaining weight loss over time remains a major barrier in the effective treatment of obesity. The NIDDK-supported Physiology of the Weight-Reduced State Consortium continues to characterize physiological mechanisms underlying individual variability in maintenance of reduced weight over time.[458] Investigators are studying adults with obesity before and after weight loss from a behavioral/lifestyle intervention to understand appetite and metabolic adaptations to reduced weight. This research may lead to novel strategies for maintaining weight loss over time.

In addition to lifestyle and behavioral approaches, scientific advances are revealing new biological mechanisms that may lead to more targeted and tolerable obesity treatments. Researchers supported by NIDDK have discovered a direct line of communication (via sensory nerve cells) between fat tissue and the brain in mice, challenging the notion that circulating hormones in the blood are the sole messengers sending information related to stress and metabolism between fat cells and brain cells.[459] This finding fills a critical knowledge gap on how the brain regulates fat tissue, which could potentially lead to new therapeutic strategies to treat obesity. In another NIDDK-supported study, looking at the effects of new obesity medications on the brain in mice, researchers discovered that the therapeutic benefits of the medications can be successfully uncoupled from the adverse side effects because different populations of brain cells control food intake and nausea.[460] Because nausea is a side effect of many treatments for multiple diseases, this new insight could be applied to investigate therapies beyond those for obesity with a goal of developing more targeted drugs that treat disease but avoid negative side effects.

[456] Manoogian ENC, et al. Cell Metab. 2022 Oct 4;34(10):1442-1456.e7. PMID: 36198291.
[457] Pavlou V, et al. JAMA Netw Open. 2023 Oct 2;6(10):e2339337. PMID: 37889487.
[458] https://www.powers-study.org/
[459] Wang Y, et al. Nature. 2022 Sep;609(7927):569-574. Epub 2022 Aug 31. PMID: 36045288.
[460] Huang KP, et al. Nature. 2024 Aug;632(8025):585-593. Epub 2024 Jul 10. PMID: 38987598.

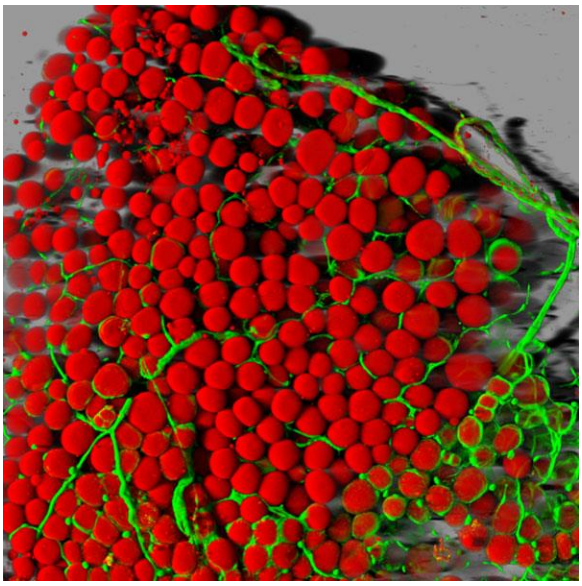


Figure 26. A mouse's fat cells (red) are shown surrounded by a network of blood vessels (green). Credit: Daniela Malide, NHLBI/NIH

Behavioral Science and Long-term Weight Management

Understanding and supporting long-term health behavior change is a cornerstone of preventing and managing chronic diseases, including obesity. OBSSR and the Adherence Research Network Scientific Interest Group, a multidisciplinary consortium of NIH ICOs, have adopted health behavior maintenance as a major scientific focus, crucial for managing chronic illness treatment and prevention of disease. Since 2022 they have jointly led activities to review the state of the science of health behavior maintenance and identify opportunities for development of effective long term health behavior change interventions to improve public health.[461] The scientific focus will lead to improved health outcomes for all persons, beyond just those with obesity.

In parallel, NIH-supported research is uncovering how biological rhythms influence key health behaviors, offering new insights into how behavior and physiology interact in the context of obesity. NHLBI-funded researchers examined the relationship between obesity and sleep. They found that in people without obesity, energy metabolism is lowest at night during sleep; while in people with obesity, it is lowest during the day.[462] This means that people with obesity showed heightened glucose intolerance during the day and produced less insulin at night, which may not align with biological energy needs. This research highlights new approaches, as described in the NIH Sleep Research Plan, that focus on circadian rhythms and the timing of biological processes to prevent chronic disease and poor health outcomes. These efforts illustrate the critical role of behavioral science and biological timing in designing sustainable interventions that align with how people live, sleep, and manage their health over the long term.

Diet, Nutrition, and the Food Environment

[461] https://obssr.od.nih.gov/about/health-behavior-maintenance
[462] McHill AW, et al. Obesity (Silver Spring). 2024 Feb;32(2):315-323. Epub 2023 Nov 15. PMID: 37964700.

Poor nutrition is now the leading cause of poor health outcomes and preventable death in the U.S., driving chronic disease and escalating health care costs—making diet, food environments, and nutrition-focused interventions central to improving public health.[463] Poor diets also exacerbate health differences between populations, as exemplified by individuals with lower incomes, individuals living in rural communities, and those from historically marginalized racial and ethnic groups all being more affected. Moreover, poor diets are harming the U.S economy in that the combined health care spending and lost productivity from poor diets are estimated to cost over $1 trillion each year. Yet a focus on nutrition is currently missing in the health care system. The Food is Medicine Networks and Centers of Excellence Program is an NIH-wide, nutrition-focused initiative that will support programs that respond to the critical link between diet and health with the provision of healthy food, as well as having health care organizations as their nexus.[464,465] The program will address current barriers that exist both in communities and within health care systems that severely limit the ability to reduce obesity and other diet-related diseases such as cardiovascular disease, cancer, and diabetes; and it will support implementation science and intervention and health quality research strategies to improve public health and address barriers to care.

Efforts to transform the health system through food-based care are strengthened by foundational research into how diet quality influences chronic disease and how to create effective, evidence-based eating patterns. The NHLBI-sponsored Dietary Approaches to Stop Hypertension diet was ranked the "Best Heart-Healthy Diet" and "Best Diet for High Blood Pressure" in the *2025 Best Diets report from U.S. News & World Report*.[466] To receive top rankings, a diet must be nutritious, safe, easy to follow, effective for weight loss, and protective against diabetes and heart disease. The diet, which builds nutrient-dense meals around whole grains, vegetables, and fruits, and includes fish, poultry, beans, nuts, and healthy oils, was also rated the third "easiest diet to follow."

Researchers are also exploring how the broader food environment—including where and how people access food—shapes dietary habits and disease risk. Research suggests an individual's food environment, defined as the spaces where people obtain and consume foods, can affect their health. However, much food environment research to date has been limited to studying areas near people's homes. Researchers funded by the NIH Common Fund program Nutrition for Precision Health, powered by the *All of Us* Research Program, examined whether large-scale smartphone geolocation data that tracked people's movement throughout the day could be used to measure fast food intake, which is a marker of people's dynamic use of food environments.[467] The study found that this mobility data was a better predictor of obesity and diabetes than self-reported fast-food intake. These findings indicate that the use of large-scale mobility data may be a valid approach to research diet and its impact on health and chronic disease.

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[463] Matthews ED, et al. Front Public Health. 2024 May 16;12:1339859. PMID: 38827626.
[464] Lynch CJ. Am J Clin Nutr. 2023 Jul;118(1):10-12. Epub 2023 Apr 25. PMID: 37105523.
[465] https://dpcpsi.nih.gov/sites/default/files/Day-1-155PM-ONR-Concept-Food-is-Medicine-Lynch-background-508.pdf
[466] https://www.nhlbi.nih.gov/news/2025/nih-supported-dash-diet-named-best-heart-healthy-diet-and-best-diet-high-blood-pressure
[467] Horn AL, et al. NPJ Digit Med. 2023 Nov 15;6(1):208. PMID: 37968446.

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. 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.

Multiple NIH ICs support research on palliative care relevant to their unique research and disease portfolios. However, a centralized NIH approach would help identify synergies among these ICs and create a clearer training path for those interested in research careers in this area. NIA was recently named the lead NIH IC for this effort and coordinated a new funding opportunity to develop the Consortium for Palliative Care Research Across the Lifespan.[468,469] The initiative is also supported by NCI, NICHD, NIMH, NINDS, and NINR, with additional ICs contributing expertise and programmatic support. The consortium will: generate new scientific knowledge through pilot and exploratory studies awarded through national, peer-reviewed competitions; foster training and mentoring of early- and mid-career investigators through its Research Education Core Scholars program and other activities; engage health care systems and community-based organizations as research partners and settings; facilitate research to understand and address differences in access, quality, and use of palliative care services between populations; and disseminate research findings, best practices, data, and other impactful resources to the palliative care research and clinical communities.

Previous research suggested benefits of palliative care such as reduced hospital stays and costs. However, many people either do not get referred to palliative care or receive it late in their illness. An NIA-funded study found that automatically ordering palliative care for seriously ill hospitalized patients increased consultation rates and expedited the timing of consultations, but did not reduce the length of hospital stays.[470] The study, conducted across 11 community hospitals, included 34,239 participants aged 65 and older with serious illnesses, divided into groups receiving either default palliative care consults or usual care. Results showed that 43.9 percent of patients with default orders received palliative care consultations compared to 16.6 percent in the usual care group, with consultations occurring over a day sooner for the default group. Despite the higher consultation rates and improved timing, there was no difference in hospital stay length or in-hospital mortality between the groups, though default orders did lead to higher rates of do not resuscitate orders and hospice transfers. Study suggests that default palliative care could be a valuable tool for health systems to enhance the delivery of guideline-recommended clinical consultations, even though it may not influence hospital stay length.

Pulmonary Diseases

Many different types of pulmonary diseases affect the lungs and respiratory system. For example, Chronic obstructive pulmonary disease (COPD), which prevents airflow to the lungs and causes breathing

[468] https://www.nia.nih.gov/research/blog/2024/02/nia-leading-efforts-coordinate-nih-palliative-care-research
[469] https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-25-002.html
[470] Courtright KR, et al. JAMA. 2024 Jan 16;331(3):224-232. PMID: 38227032.

problems, has been diagnosed in more than 16 million Americans.[471] Lung health and sleep are linked in complex ways. People with lung disease often have trouble sleeping. Sleep apnea occurs when a person has one or more pauses in breathing or shallow breaths while sleeping. Around 50 to 70 million Americans suffer from a sleep disorder, which in turn, can increase a person's risk for other health issues.[472] 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.

Understanding Lung Biology and Pulmonary Diseases

While procedures such as MRI and CT scans can suggest when a patient has lung disease or illness, these techniques fail to provide the real-time information that is key to understanding the intricate workings of the lung at the cellular resolution. NHLBI sponsored new technology for studying the mouse lung ex vivo—or outside of the body—while it is still breathing and supplied with a blood supply. The technology relies on a never-before-seen protective shield called the crystal ribcage, a clear structure that has similar properties of the lab mouse ribcage and allows researchers to image the mouse lung in real time.[473] This is important because the crystal ribcage allows researchers to witness the moment-to-moment dynamics of respiration and circulation, the body's response to airborne pathogens, and what happens when tumor and immune cells move into the lungs.

The goal of the Molecular Atlas of Lung Development Program is to improve our understanding of human lung development.[474] The program is an open-access reference resource of a comprehensive, dynamic, 3D molecular atlas of the late-stage developing human lung with data and reagents available to the research community. It uses cutting-edge technology and precision medicine to create an open-source atlas of the lung that includes both molecular and cellular maps of the organ. Program researchers recently reported the creation of the first molecular map of human newborn lung cells by using sophisticated laboratory techniques that determine the specific genes that are turned on in individual cells. Data from molecular maps of mouse lungs were also used to estimate the maturation states of the human cells.

A recent study conducted by NHLBI-supported researchers examined the link between the body's circadian rhythms and the development of lung diseases. The study, using observations from mice and human subjects, has uncovered a new mechanism underlying the link—a circadian rhythm protein called REV-ERBα.[475] A lack of REV-ERBα contributes to lung scarring in mouse models by increasing production of collagen, a major component of connective tissue, and the enzyme lysyl oxidase, which makes connective tissue more rigid. Thus, REV-ERBα appears to be an important molecular regulator of fibrotic progression in the lungs and could become a future drug target for new treatments.

NHLBI has partnered with the COPD Foundation to support the Subpopulations and Intermediate Outcome Measures in COPD Study of Early COPD Progression, which began recruiting participants in 2022.[476] This

[471] https://www.cdc.gov/copd/index.html
[472] https://www.nhlbi.nih.gov/health/sleep-apnea\
[473] https://www.nhlbi.nih.gov/news/2023/watching-lungs-work-through-crystal-ribcage
[474] https://www.lungmap.net/
[475] Prasad C, et al. Biochem Biophys Res Commun. 2023 Aug 20;669:120-127. PMID: 37269594.
[476] https://sourcestudy.net/source/

observational study aims to define the nature of early COPD in younger, at-risk individuals. This is important because most of what we know about COPD comes from research about its later stages. However, many experts believe the best chance to slow or halt the progression of COPD involves targeting mechanisms at the earliest stages of the disease.

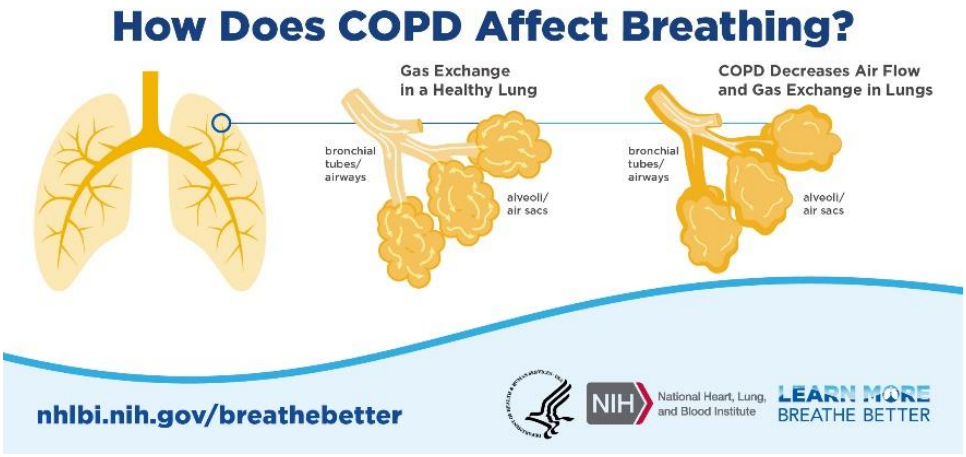


Figure 27. Chronic Obstructive Pulmonary Disorder (COPD) affects breathing by decreasing the air flow and gas exchange in the lungs. Credit: NHLBI/NIH

Advancing Treatments for Pulmonary Diseases

The NHLBI-funded Prevention and Early Treatment of Acute Lung Injury network is a network of clinical centers that developed and conducted randomized controlled clinical trials to prevent, treat, and/or improve the outcome of patients who have, or who are at risk for, Acute Lung Injury or Acute Respiratory Distress Syndrome.[477] From 2013 to 2023, the network successfully conducted five major randomized controlled trials, conducted various observational studies, and aided in the development of therapeutic interventions. One of the network's clinical trials found that intravenous acetaminophen (a common ingredient in pain relief medicines such as Tylenol) reduced sepsis patients' risk of organ injury or developing acute respiratory distress syndrome, a serious condition that allows fluid to leak into the lungs.[478] These findings show great promise for patients who become critically ill with sepsis. Another achievement of the network is that clinical trial data and remaining biospecimens for all but the most recent network trial are available to the public through the Biologic Specimen and Data Repository Information Coordinating Center.[479]

The Strategies to Innovate Emergency Care Clinical Trials Network is a clinical trials network led by NINDS, NHLBI and NCATS.[480] The goal of the network is to improve the outcomes of patients with neurologic, cardiac, respiratory, and hematologic emergencies by identifying effective treatments given in the earliest stages of care. The international multicenter clinical trials network of physicians and researchers aims to

[477] https://petalnet.org/index.html
[478] Ware LB, et al. JAMA. 2024 Aug 6;332(5):390-400. PMID: 38762798.
[479] https://biolincc.nhlbi.nih.gov/home/
[480] https://siren.network/

study what treatments work best for patients with emergency conditions or injuries. Emergencies may involve heart, lung, or blood conditions, problems or injuries involving the brain or spinal cord, seizures, coma, or other traumatic injuries. The network studies patients in ambulances and emergency departments, and the earliest stages of critical care, because many promising treatments may only work well if they are given very quickly after the onset of symptoms or injury.[481]

Lung transplantation is a life-saving intervention for many individuals, but this treatment risks serious complications, including infection and donor organ rejection. One-third to one-half of transplant patients develop treatable acute cellular rejection in the first year after transplantation, which can lead to chronic lung allograft dysfunction, a progressive syndrome that is the most common cause of mortality and morbidity in lung transplant recipients. To identify who was likely to develop chronic lung allograft dysfunction after acute cellular rejection, NHLBI researchers examined recipients' blood for cell-free DNA, which is released into the bloodstream when a cell dies.[482] An increase in the relative amounts of donor-derived cell free DNA indicates either rejection or infection of the donated tissue. Researchers found that patients with a high concentration of donor-derived cell free DNA at the time of acute cellular rejection had an increased risk of both chronic lung allograft dysfunction and death, independent of the severity of the acute cellular rejection episode.

More than 1.5 million Americans use supplemental oxygen for a range of medical conditions. Yet some patients have found that portable oxygen creates challenges with daily activities, exercise, socialization, work, and travel. Through the Air You Wear Challenge prize competition,[483] NHLBI aimed to broadly stimulate the research and development of processes and technologies designed to improve the accessibility, efficacy, and usability of supplemental oxygen. In February 2023, NHLBI named three winning teams and one honorable mention. Since then, two teams successfully completed the competitive NIBIB 2022-2023 Concept to Clinic: Commercialization Innovation program, and all three winners have submitted small business applications to help conduct pre-clinical and/or clinical feasibility studies.

Through its Learn More Breathe Better program,[484] NHLBI supports community organizations working to raise COPD awareness, including a new effort to reach rural healthcare providers in the Appalachian region. In collaboration with the Respiratory Health Association, NHLBI's Learn More Breathe Better program launched the COPD Caregiver's Toolkit in 2022. This resource addresses the top issues that COPD patients and caregivers face, including home management, physician visit preparation, and emergency preparedness.

Substance Misuse and Addiction

A range of substances, including nicotine, cannabinoids, alcohol, opioids, depressants, stimulants, and hallucinogens, continue to be misused, and may lead to addiction for many people. According to the 2023 National Survey on Drug Use and Health, among Americans aged 12 or older, 59.0 percent (around 167.2 million people) used tobacco, vaped nicotine, used alcohol, or used an illicit drug in the past month. In the

[481] https://reporter.nih.gov/search/8vFkXT5MbkuODMRlEUYDpw/project-details/10550501
[482] Keller M, et al. J Heart Lung Transplant. 2022 Apr;41(4):458-466. PMID: 35063338.
[483] https://www.nhlbi.nih.gov/grants-and-training/air-you-wear-challenge
[484] https://www.nhlbi.nih.gov/BreatheBetter

past year, among Americans aged 12 or older, 10.2 percent (around 28.9 million people) had alcohol use disorder, 9.6 percent (around 27.2 million people) had at least one illicit drug use disorder, 1.9 percent (around 5.3 million people) had a prescription pain reliever use disorder, and 2.0 percent (around 5.7 million people) had an opioid use disorder.[485,486] Individuals living with substance use disorders (SUDs) are also at particular risk for developing comorbid chronic health conditions, including chronic pain, cancer, and heart disease. The presence of a mental disorder may contribute to the development or exacerbation of an SUD; likewise, the presence of an SUD may contribute to the development or exacerbation of another co-occurring mental disorder. The combined presence of SUDs and other comorbid mental disorders results in more profound functional impairment; worse treatment outcomes; higher morbidity and mortality; increased treatment costs; and higher risk for homelessness, incarceration, and suicide. From the same 2023 National Survey on Drug Use and Health, among U.S. adults with a mental illness, about one third (around 20.4 million people) had an SUD. Substance misuse also causes an economic burden—the annual cost of substance misuse in the U.S. 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.[487]

Despite affecting tens of millions of people each year and contributing to decreased quality of life and increased morbidity and mortality, only 4.5 percent (around 12.8 million people) of U.S. adults received substance use treatment in the past year.[488]Although many challenges remain, groundbreaking research and discoveries about the brain have revolutionized how alcohol and drug addictions are understood and treated. NIDA is the lead NIH IC for research on drug use and addiction; though several ICOs across NIH focus on aspects of substance misuse and addiction, such as NIAAA's efforts to prevent underage drinking. NIH 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, prevention, and recovery. NIH also supports research training, career development, public education, public-private partnerships, and research dissemination efforts.

Opioid Use Disorder

Opioid use disorder (OUD) is a chronic health condition that involves a problematic pattern of opioid use and can have serious and life-threatening consequences, such as overdose and death. Opioid overdoses continue to be a serious public health challenge, and the advent of more powerful synthetic opioids is only adding more urgency to finding solutions to prevent overdose. A study on intranasal nalmefene

[485] https://nsduhweb.rti.org/respweb/homepage.cfm
[486] Key Substance Use and Mental Health Indicators in the U.S.: Results from the 2023 National Survey on Drug Use and Health (https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annual-national.pdf)
[487] https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/index.html
[488] Key Substance Use and Mental Health Indicators in the U.S.: Results from the 2023 National Survey on Drug Use and Health (https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annual-national.pdf)

administration led by NIDA resulted in FDA approval of Opvee in 2023.[489] This formulation of nalmefene offers a faster onset and longer duration of action compared to naloxone, enabling the reversal of overdoses involving long-acting synthetic opioids such as fentanyl.[490,491] Nalmefene provides a valuable new tool for addressing the overdose crises, especially in emergency situations. It has been approved for prescription use and enhances the armamentarium available to healthcare providers and first responders.

Medications are not the only means of treating opioid overdoses and preventing death. The hallmark symptom of an opioid-related overdose is decreased respiration, which can result in permanent hypoxic brain injury within minutes. In 2023, NIDA-supported researchers developed an Automated External Respiration System, which is a community-deployable wearable device that stimulates the phrenic nerve—which provides motor control of the diaphragm, the primary muscle of respiration—externally, to maintain adequate respiration during opioid-induced respiratory depression. The concept is modeled after Automated External Defibrillator devices, which are widely available in medical and public settings for use by both medically trained and untrained individuals. The researchers recently submitted an Investigational Device Exemption to the FDA for approval to test the device.

NIDA-funded researchers are developing and refining a prehospital, Emergency Medical Services clinical field protocol to initiate buprenorphine in persons with OUD presenting with a severe overdose (e.g., requiring naloxone rescue) or acute opioid withdrawal, where symptoms are sudden and intense and often require medical intervention.[492] The goal is to provide rapid medication access and collect preliminary feasibility, acceptability, and safety data. A multi-site evaluation trial will also be conducted to examine the rates of engagement in continuation of medication for OUD post-emergency medical services initiation.

In addition to medications for immediate, life-saving intervention during an opioid overdose (e.g., naloxone), NIH supports research into medications for OUD, which are used for long-term management and relapse prevention. This typically involves the use of medications, such as buprenorphine, in combination with counseling and behavioral therapies. For example, NIDA and the NIH HEAL Initiative support research into methocinnamox as a novel opioid receptor blocker with pharmacological properties that could make it useful for treating OUD (i.e., preventing relapse) and overdose. A single dose blocks the abuse-related and toxic effects of opioids for weeks in rats and nonhuman primates.[493,494,495,496] An initiative is underway to further develop methocinnamox for preventing opioid relapse and sustain abstinence after detoxification, and an Investigational New Drug (IND) application to the FDA is planned for 2025 for permission to begin testing a new medicine in people for the first time.

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[489] https://www.fda.gov/news-events/press-announcements/fda-approves-prescription-nasal-spray-reverse-opioid-overdose
[490] Ellison, M., et al. J Clin Pharmacol. 2024 Jul;64(7):828-839. PMID 38436495.
[491] Crystal, R., et al. Clin Pharmacol Drug Dev. 2024 Jan;13(1):58-69. PMID 37496452.
[492] https://nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/ems-initiated-buprenorphine-opioid-use-disorder
[493] Maguire, D. R., et al. J Pharmacol Exp Ther. 2022 Aug;382(2):181-187. PMID 35643857.
[494] Maguire, D. R., et al. Neuropharmacology. 2024 Feb 1;243:109777. PMID 37944894.
[495] Maguire, D. R., et al. J Exp Anal Behav. 2023 Mar;119(2):392-406. PMID 36759567.
[496] Jordan, C. G., et al. Pharmacy (Basel). 2022 Apr 19;10(3):48. PMID 35645327.

With funding from NIDA, a small drug company began the first in human Phase 1 clinical study to evaluate the safety, tolerability, and pharmacokinetics of CSX-1004, a fully human monoclonal antibody against fentanyl and fentanyl analogs. The antibody's long duration of action offers promise of preventing renarcotization—the phenomenon where the effects of opioids return—after overdose reversal, a potential concern with short-acting reversal agents.[497,498] It could also help in preventing additional overdose episodes in the days and weeks after release from the emergency department when patients are particularly vulnerable to relapse.

Not all communities are similarly affected by the public health crisis of opioid misuse, addiction, and overdose. The HEALing Communities Study, launched by NIDA and the Substance Abuse and Mental Health Services Administration in 2019, assessed a community-wide approach to reduce overdose deaths by deploying evidence-based strategies to widen distribution of naloxone and expand access to medications for OUD. The study took place in 67 communities in Kentucky, Massachusetts, New York, and Ohio; four states disproportionately affected by opioid overdose deaths. Findings will help establish best practices for integrating prevention and treatment strategies that can be adapted by communities nationwide.

Opioid withdrawal refers to symptoms that happen once opioid use is suddenly stopped and occurs because people become physically dependent on the drugs. Opioid withdrawal is not typically life-threatening, but it can make the individual feel very sick. CVL-354 is a selective kappa opioid receptor blocker developed by a small drug company with support from NIDA.[499] Phase 1 studies showed it to be safe and well-tolerated, with confirmed target engagement in a receptor occupancy study. The compound shows promise in alleviating withdrawal symptoms for individuals with OUD.

NIH supports a variety of research on medications for OUD, including different types and combinations of medications and strategies for administering treatment. Emergency department-initiated buprenorphine treatment with referral for ongoing treatment is superior to referral alone in engaging patients with untreated OUD and is cost effective. However, barriers exist in translating this research into practice. The NIDA-supported Emergency Department-Initiated Buprenorphine and Validation Network Trial tested the feasibility of a 7-day injectable buprenorphine formulation in patients experiencing minimal to mild opioid withdrawal.[500] Results found that the formulation was well-tolerated, acceptable, and safe for use in individuals experiencing minimal to mild withdrawal.[501] If scaled, this approach could dramatically increase the number of patients with OUD receiving buprenorphine.

While medications for OUD are effective and beneficial, it does not treat all the symptoms of OUD, and many of those medications come with side effects of their own that present additional challenges. Thus, additional drugs may be necessary to support full recovery. Sleep problems are a common complaint among people with SUDs, including more than 75 percent of people with OUD who have sleep problems,

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[497] https://clinicaltrials.gov/study/NCT06005402?term=csx1004&rank=1
[498] Bremer, P. T., et al. Nat Commun. 2023 Dec 5;14(1):7700. PMID 38052779.
[499] https://clinicaltrials.gov/study/NCT05138653?intr=CVL-354&rank=1
[500] https://nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/emergency-department-initiated-buprenorphine-validation-network-trial-ed-innovation-nih-heal
[501] D'Onofrio, G., et al. JAMA Netw Open. 2024 Jul 1;7(7):e2420702. PMID 38976265.

such as irregular sleep schedules, not sleeping enough, and/or having a sleep disorder (e.g., insomnia, sleep apnea). They can occur during withdrawal, but they can also last months and years into recovery and can be associated with relapse. The orexin neurotransmitter system plays a role in insomnia. Suvorexant is an orexin receptor blocker that is FDA-approved for the treatment of insomnia, and preliminary data suggests that suvorexant might be efficacious in treating insomnia in persons with OUD. In May 2024, a NIDA-supported project advanced suvorexant to Phase 3 multi-site randomized-controlled trials to determine whether it is an effective treatment for insomnia in persons maintained on the medication-assisted treatments of buprenorphine or methadone.

In a related effort, NIDA's HEAL Initiative is collaborating with NHLBI to address the potential mechanisms of the relationship between sleep disturbances and SUDs and develop tools that leverage assessments of sleep parameters as indicators of recovery progress and relapse risk. Five projects were supported that are conducting clinical studies targeted at developing electroencephalography-based, sleep and circadian predictors of OUD medication treatment response and outcomes that can be rapidly translated to the clinic to predict relapse to OUD.

Buprenorphine is a leading option for medications for OUD, but many recipients have high early relapse rates possibly due to varying degrees of dysfunction within drug craving and cognitive control neuronal networks. Transcranial direct current stimulation—a non-invasive brain stimulation technique that uses low electrical currents to modulate neuronal activity—may be a promising add-on treatment to help ameliorate these challenges. NIDA-supported scientists tested the ability of transcranial direct current stimulation to reduce drug craving in buprenorphine recipients. The study successfully transitioned to the second phase with the larger clinical trial, demonstrating that it holds promise as another tool to help doctors and patients better manage OUD.

NIH also supports research on the second part of medications for OUD—counseling and behavioral therapies. With support from NCCIH and the HEAL Initiative, researchers tested the pre- and post-effects of adding the mindfulness-based intervention Mindful Awareness in Body-Oriented Therapy to the standard drug treatment for OUD. The study found that while mindful awareness therapy did not reduce substance use, it led to significant positive changes in other areas that can help improve the standard treatment.[502]

Dropout from treatment is a major barrier to the effectiveness of buprenorphine and other medications for OUD. However, evidence shows that 50 percent or more of participants drop out of treatment by 3 to 6 months and patients who do stay in treatment often eventually ask how long they need to continue medication, and whether it would be safe to discontinue. There is little evidence available to guide clinicians' responses to these questions. The NIDA and NIH HEAL Initiative study Optimizing Retention, Duration and Discontinuation Strategies for Opioid Use Disorder Pharmacotherapy addresses this by testing strategies to improve OUD pharmacotherapy treatment retention and to improve outcomes among patients who have been successfully stabilized on OUD medications and want to stop medication. In

[502] Price, C. J., et al. Mindfulness (N Y). 2024 Nov;15(11):2794-2811. PMID 39697819.

addition, the study also aims to identify predictors of successful outcomes and develop a stage model of relapse risk.[503]

Opioid misuse is the use of prescription opioids outside of medical supervision, such as taking them in larger amounts or using them for non-medical purposes, while OUD is a chronic condition characterized by a problematic pattern of opioid use that causes significant impairment or distress in daily life. Preventing the transition from opioid misuse to OUD is a key priority of NIH. Supported by NIDA and the NIH HEAL Initiative, the Subthreshold Opioid Use Disorder Prevention trial will test the efficacy of a primary care intervention to reduce opioid use and overdose risk, and prevent progression to OUD, in adults with unhealthy use of illicit or prescribed opioids.[504] The intervention, if proven efficacious, will provide a solution to preventing OUD among patients who are most at risk, thus addressing a key aspect of the current opioid crisis.

Non-Opioid Pain Relievers for Opioid Use Disorder

Safer opioids to treat severe pain while providing protection against abuse and oral overdose are another strategy to counter OUD. With support from NIDA, a small drug company developed PF614-MPAR, which shows promise for providing optimal pain relief at prescribed doses yet limit accidental or intentional overdose by 'shutting down' opioid release if too much active drug is consumed. PF614-MPAR is an oxycodone prodrug, meaning it remains pharmacologically inactive until released by trypsin (a digestive enzyme) in the digestive tract. Importantly, PF614-MPAR also contains a trypsin inhibitor which prevents release if multiple pills are ingested.[505] This novel coformulation offers an innovative approach to mitigating abuse and overdose potential. In January 2024, the compound received FDA Breakthrough Therapy Designation, a rarely used designation, having been granted to fewer than 300 drugs.[506]

Opioid pain-relieving effects are mediated by activation of the mu opioid receptor. Unfortunately, selective activation of this receptor is associated with the harmful side effects of opioids that are a leading cause of the epidemic—tolerance, dependence/addiction, and respiratory depression. Recently, activation of another receptor, called nociceptin/orphanin FQ peptide receptor, has been reported to enhance the mu receptors pain reliving effects without producing side effects. With support from NIDA, cebranopadol is being developed as a first-in-class dual mu opioid receptor and nociceptin/orphanin FQ receptor activator that can be used as a safe and alternative treatment for moderate-to-severe acute pain. Positive clinical results from an intranasal human-abuse-potential study support its low addiction potential.

Another key approach in preventing OUD is developing a new class of non-opioid pain relievers that do not pose a risk of addiction. NIDA has funded development of Kindolor and Arylepoxamide, two novel analgesics intended to prevent OUD. In June 2023, Kindolor, a multimodal, opioid-sparing treatment for

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[503] https://nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/optimizing-retention-duration-discontinuation-strategies-opioid-use-disorder-pharmacotherapy-nih

[504] https://nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/subthreshold-opioid-use-disorder-prevention-stop-trial-nih-heal-initiative

[505] Kirkpatrick, D.L., et al. Clin Transl Sci. 2024 Mar;17(3):e13765. PMID 38511523.

[506] https://ir.ensysce.com/news/press-releases/detail/139/ensysce-biosciences-announces-fda-breakthrough-therapy

pain, entered Phase 1 clinical testing.[507] Kindolor is a small molecule that reduces the over-activity of the nociceptive (pain-sensing) peripheral neural network that generates chronic pain and has negligible penetrance into the brain, thus reducing deleterious side effects. In FY24, a small drug company completed a Phase 1 study for the compound SBS-1000, an arylepoximide receptor activator, as a new class of safer analgesics. The compound was found to be safe and well-tolerated.[508] The arylepoxamide receptors are a class of receptors widely distributed throughout the brain and spinal cord and are believed to modulate pain signaling and pain perception.

Nociceptors are specialized nerve endings located throughout the body that respond to potentially damaging stimuli by sending pain signals to the brain. One class of non-opioid pain relievers are designed to target these receptors, such as by blocking specific ion channels on nociceptors, like sodium or calcium channels, which are crucial for the initiation and propagation of pain signals. With support from NIDA and the HEAL Initiative, STC-004, an oral small molecule inhibitor of the Nav1.8 sodium channel, found in nociceptors has been developed.[509] The project has completed Phase 1 trials, with plans to begin Phase 2 studies, pending FDA approval.

Taking medications are not the only avenue available for non-opioid pain control. Auriculotherapy, a form of acupuncture, could be an effective alternative to treat pain if challenges associated with wider adoption of it—like long and specific training requirements—are overcome. NIDA-supported researchers are assessing the use of a battery-powered, disposable auricular nerve stimulator for its capacity to reduce opioid consumption following open surgery in adults and geriatric patients. The study, which began in FY22, also investigates the device's effect on post-operative symptoms including anxiety, depression, and catastrophizing of pain.[510,511]

Substance Use Disorder Involving Non-Opioids

While OUD and opioid overdoses receive a lot of attention, according to the 2023 National Survey on Drug Use and Health, among Americans aged 12 or older, while just 2.0 percent (around 5.7 million people) had an OUD, 9.6 percent (around 27.2 million people) had at least one illicit drug use disorder.[512] NIH supports research on preventing and treating a wide variety of SUDs. Methamphetamine is a highly addictive central nervous system stimulant associated with a range of negative health outcomes, including damage to the heart and brain, anxiety, confusion, insomnia, mood disturbances, and violent behavior. In August 2023, with support from NIDA, a small drug company developed a sequestrant, CS-1103, to clear

[507] https://lohocla.com/media/pdf/LohoclaResearch_Kindolor_Phase1-trials_PRESS_RELEASE.pdf
[508] https://www.sparianbiosciences.com/news/sparian-biosciences-announces-results-from-the-phase-1-clinical-trial-of-first-in-class-novel-arylepoxamide-receptor-aear-agonist-analgesic-sbs-1000/
[509] https://www.businesswire.com/news/home/20250204089126/en/SiteOne-Therapeutics-Announces-Positive-Phase-1-Clinical-Data-for-STC-004-a-Novel-NaV1.8-Inhibitor-in-Development-for-the-Non-Opioid-Treatment-of-Pain
[510] Chen, Y. H., et al. Expert Rev Clin Pharmacol. 2023 Jul-Dec;16(9):813-823. PMID 37531096.
[511] Kocher, M., et al. Children (Basel). 2024 Mar 20;11(3):368. PMID 38539403.
[512] Key Substance Use and Mental Health Indicators in the U.S.: Results from the 2023 National Survey on Drug Use and Health (https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annual-national.pdf)

methamphetamine from the body.[513] The injectable small molecule sequestrant works by immediately binding to and inactivating target compounds, rapidly reversing their toxic effects and accelerating clearance into urine. The compound has completed Phase 1 testing and was shown to be safe and well-tolerated.

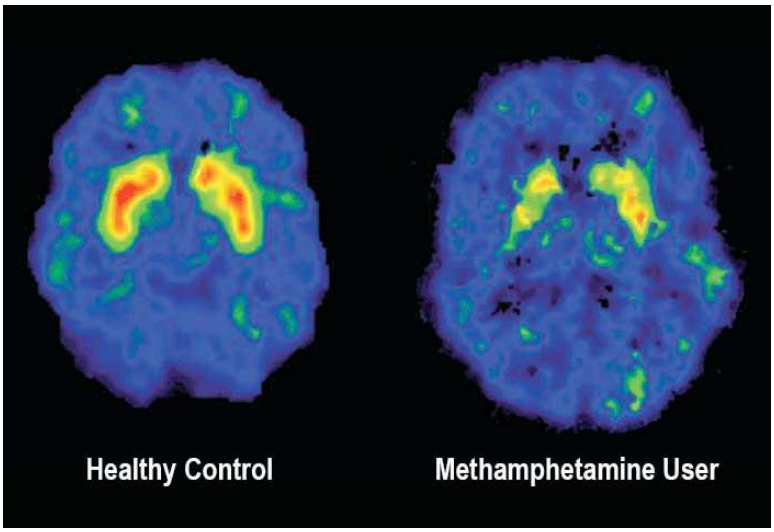


Figure 28. A brain scan of a methamphetamine user compared to a healthy individual. Methamphetamine abuse decreases dopamine transporter activity and compromises mental function. Credit: NIDA/NIH

Cannabis, more commonly known as marijuana, refers to the dried flowers, leaves, stems, and seeds of the cannabis plant, which contains more than 100 compounds (or cannabinoids), including tetrahydrocannabinol, which is impairing or mind-altering and the primary psychoactive component of cannabis. Although there are medicinal uses for cannabis (e.g., to treat nausea in patients with cancer who are having chemotherapy treatment), it also has many adverse health effects, including cannabis use disorder where people who use cannabis, especially newer products with highly concentrated tetrahydrocannabinol, struggle with physical dependency and controlling their use. The recent increase in cannabis legalization in regions around the country—while still illegal federally, it is fully legal in about half of the 50 states—only adds to the need to develop effective preventive measures and effective treatments for cannabis use disorder. NIH supports research in this area. For example, NIDA and HEAL Initiative-supported scientists are examining if transcranial direct current neurostimulation paired with reappraisal training will enhance emotional regulation, resulting in a reduction of cannabis use. The study will also set the stage for future work in larger samples and longer durations investigating neurostimulation as a method to augment treatment for cannabis use disorder.

Cocaine use is a major public health concern, leading to increased morbidity, premature mortality, and severe social consequences both for the individual and for society. Despite the widespread use of cocaine and the resulting negative consequences, there are currently no approved medications for the treatment of cocaine use disorder. In April 2024, NIDA-supported scientists initiated a double-blind, placebo-

[513] https://www.clearsci.com/post/clear-scientific-reports-positive-topline-phase-1-clinical-trial-data-for-cs-1103

controlled, parallel group study to compare the effects of STP7 (mavoglurant) versus placebo on intravenous cocaine's physiological and subjective effects.[514] The primary objective is to determine if there are clinically meaningful interactions between oral mavoglurant treatment concurrent with cocaine infusions by measuring adverse events and cardiovascular responses.

In a related study, also supported by NIDA, researchers initiated a double-blind, placebo-controlled, parallel group study to compare the effects of SXC-2023 versus placebo on intravenous cocaine's physiological and subjective effects in non-treatment seeking cocaine-experienced participants.[515] The goal is to determine whether there are any interactions between the study drug and cocaine by comparing a treatment group and a placebo group to see if they experience any effects when administered cocaine after taking the treatment or placebo.

Recent research suggests that a kappa opioid receptor blocker can curb the negative emotional states associated with stimulant withdrawal that leads to increased craving and drug-seeking behaviors. The NIDA-supported Randomized, Placebo-Controlled Trial of Injectable Naltrexone and Monthly Injectable Buprenorphine for Cocaine Use Disorder study aims to assess the safety and efficacy of combined monthly injections of extended-release naltrexone and injectable buprenorphine for cocaine use disorder. This study builds on prior work from the Cocaine Use Reduction with Buprenorphine study[516] and investigates a dual-medication strategy and expands knowledge on how treatments developed for OUD can also be applied to other SUDs.

Scientists are also exploring neuromodulation techniques to treat cocaine use disorder. Researchers supported by NIDA and the HEAL Initiative are evaluating the use of transcranial focused ultrasound—a non-invasive neuromodulation technique that uses focused ultrasound waves to modulate brain activity—to target deep brain structures implicated in cocaine use disorder. If successful, the study will pave the way for the development of chronic, repeated administration of this neuromodulation technique to treat cocaine use disorder.

Substance Use Disorders in Mothers and Newborns

SUD is especially detrimental when it occurs in pregnant mothers, with the potential for life-long consequences in children born to mothers with SUD. OUD in pregnant mothers is a serious public health challenge; from 2010 to 2017, the number of women with opioid-related diagnoses at delivery hospitalization increased by 131 percent.[517] NIH has many research efforts underway to overcome this concerning public health problem. The Medication Treatment for Opioid-dependent Expecting Mothers study, funded by NIDA and the NIH HEAL Initiative, is evaluating the comparative effectiveness of two buprenorphine formulations—extended-release and sublingual (under the tongue)—on maternal-infant

[514] https://www.clinicaltrials.gov/study/NCT06273540?term=STP7&rank=1
[515] https://www.clinicaltrials.gov/study/NCT06343532?term=SXC-2023&rank=1
[516] https://nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/randomized-placebo-controlled-trial-injectable-naltrexone-monthly-injectable-buprenorphine-cocaine
[517] https://www.cdc.gov/maternal-infant-health/pregnancy-substance-abuse/index.html

outcomes in pregnant women with OUD.[518] It also tests a conceptual model to understand the mechanisms by which extended-release buprenorphine may improve outcomes relative to sublingual.

Newborns exposed to opioids during pregnancy are at risk for a condition called neonatal opioid withdrawal syndrome, or NOWS. In the U.S., at least one newborn is diagnosed with NOWS every 24 minutes. NOWS symptoms typically include tremors; excessive crying and irritability; and problems with sleeping and feeding. To date, there has been limited generalizable evidence to support a standard of care for infants with NOWS, and treatment often involves pharmacological management with tapering opioid doses.

Funded through the NIH HEAL Initiative, the Advancing Clinical Trials in Neonatal Opioid Withdrawal research program aims to test the ways babies with NOWS are assessed, treated, and followed long-term, so that the infants can get the best possible care. One study under that program—Eating, Sleeping, Consoling for Neonatal Withdrawal: a Function-Based Assessment and Management Approach—is testing whether the "Eat, Sleep, Console" (ESC) care approach is more effective than usual approaches to assess and manage care for opioid-exposed newborns.[519] The traditional approach, used for the past 50 years, to assess and manage newborns who were exposed to opioids during pregnancy is called the Finnegan Neonatal Abstinence Scoring Tool. ESC, a newer approach, prioritizes and emphasizes nonpharmacologic care, including increased family presence, holding, swaddling, and rocking in low-stimulus environments, as first line treatment. NICHD and NIH Environmental influences on Child Health Outcomes (ECHO) Program-supported researchers found that the ESC care approach was more effective than the Finnegan Scoring Tool and showed that infants cared for with ESC were medically ready for discharge from the hospital almost a week earlier than those who received traditional care. They were also less likely to receive opioid treatment to manage their withdrawal symptoms. These findings support use of ESC as a standard treatment approach, reducing variability in care and improving outcomes. [520,521] A two-year follow-up study of a subset of infants is ongoing.

Building infrastructure and training the next generation of scientists in the field of SUD is essential to ensuring ongoing discoveries and future treatments for SUD. For example, NCATS' CTSA-supported training generated entrepreneurial impact through the development of a potential NOWS therapy.[522] Postdoctoral fellows identified a deuterated (when one or more of the hydrogen atoms in the molecule is replaced by the heavier isotope deuterium) form of buprenorphine thought to alter its metabolism to minimize formation of a harmful metabolite that contributes to NOWS, while still treating opioid-dependence and preventing relapse in the mother.[523] From this training support, the postdoctoral fellows have gained

[518] https://nida.nih.gov/about-nida/organization/cctn/ctn/research-studies/medication-treatment-opioid-dependent-expecting-mothers-moms-pragmatic-randomized-trial-comparing
[519] https://echochildren.org/act-now/
[520] Young, L. W., et al. N Engl J Med. 2023 Jun 22;388(25):2326-2337.PMID 37125831.
[521] Devlin, L. A., et al. JAMA Pediatr. 2024 Jun 1;178(6):525-532. PMID 38619854.
[522] https://news.uams.edu/2023/05/24/uams-tri-training-program-helps-postdocs-develop-entrepreneurial-spirit-form-competition-winning-pharmaceutical-startup/
[523] Janganati, V., et al. Front Pharmacol. 2023 May 9;14:1123261. PMID 37229250.

entrepreneurial experience, forming a company to bring deuterated buprenorphine through the drug development pipeline, and have been successful in several business plan prize competitions.



Figure 29. Clinical and Translational Science Award (CTSA) Program researchers viewing nucleic acids on an electrophoresis gel, a technique used to separate and analyze biomolecules, such as DNA or RNA, based on their size. Credit: NCATS/NIH

Fetal Alcohol Spectrum Disorder (FASD) refers to the collective physical, behavioral, and cognitive impairments that occur due to prenatal alcohol exposure. Up to 1 in 20 U.S. school-aged children may have FASD, and research indicates that individuals with FASD can continue to experience impairments and develop additional health conditions later in life.[524] NIAAA leads the Interagency Coordinating Committee on FASD to foster cooperation, collaboration, and communication among disciplines and federal agencies on issues related to prenatal alcohol exposure.[525] NIAAA also supports a robust FASD research program, which includes the Collaborative Initiative on Fetal Alcohol Spectrum Disorders, a multidisciplinary consortium of domestic and international researchers that focuses on improving the diagnosis, prevention, and treatment of FASD. A recent consortium study found that middle-aged adults with a history of prenatal alcohol exposure had lower cognition scores than those without alcohol exposure, suggesting that cognitive deficits from prenatal exposure do not improve with age.[526] This study highlights the need for support for individuals with FASD into adulthood. NIAAA is also facilitating development of a consensus classification system to harmonize research efforts and accelerate progress in FASD early detection, diagnosis and treatment.[527] The importance of this effort is emphasized by recent research findings that found three commonly used FASD diagnostic systems had large differences in the number of individuals classified as having FASD.

Alcohol Use Disorder

[524] https://www.cdc.gov/fasd/data/index.html
[525] https://www.niaaa.nih.gov/interagency-coordinating-committee-fetal-alcohol-spectrum-disorders
[526] Shapiro Z.R., et al. Alcohol Clin Exp Res (Hoboken). 2023 Oct;47(10):1978-1988. PMID: 37864533.
[527] Coles C.D., et al. Alcohol Clin Exp Res (Hoboken). 2023 Feb;47(2):370-381. PMID: 36521847.

Alcohol use disorder (AUD) is a medical condition characterized by an impaired ability to stop or control alcohol use that can manifest as mild, moderate, or severe and may include symptoms such as cravings, withdrawal symptoms, and continued use despite negative impacts on social and occupational functioning. AUD increases the risk of many health issues, including liver disease, heart disease, and cancers. According to the 2023 National Survey on Drug Use and Health, in the past year, among Americans aged 12 or older, 10.2 percent (28.9 around million people) had AUD.[528] Currently there are three medications approved for AUD in the U.S. In FY22, a translational study supported through a collaboration between NIAAA and NIDA, showed evidence that spironolactone, a medication currently prescribed for heart problems and high blood pressure, may play a role in reducing alcohol drinking.[529] Another collaborative study performed by NIAAA and NIDA intramural researchers found that the medication semaglutide, typically prescribed for diabetes and obesity, may be useful for curbing overall alcohol intake and treating AUD.[530] Discovering new uses for approved medications, which are already shown to be safe, provides the opportunity to expand the menu of evidence-based medications for AUD.

Alcohol misuse exacerbates more than 200 diseases and conditions. NIAAA supports many efforts focused on the mechanisms through which alcohol misuse contributes to diseases, such as cardiovascular disease, alcohol-associated liver disease, cancer, and dysfunction of the lung, pancreas, gut, immune system, and skeletal muscle.[531] For example, in a recent study, researchers identified 10 molecules in the body associated with long-term alcohol consumption and cardiovascular disease risk. The Alcohol-Associated Hepatitis Network is a coordinated network of translational and clinical research studies across 12 institutions that aims to better understand the biology and treatment of alcohol-associated hepatitis.[532] In 2022, NIAAA sponsored a workshop to bring together alcohol-associated liver disease researchers and specialists to inform improved integrated care for patients, laying the groundwork for future clinical trials focused on evaluating the impact of integrated care. And in 2024, NIAAA held another workshop on the prevention of alcohol-associated liver disease through early detection and screening, highlighting pathways for inter-specialty care delivery.[533]

Decades of research have firmly established the importance of asking primary care patients about their alcohol use, providing brief advice about reducing alcohol misuse, and referring them to appropriate alcohol treatments, as necessary. Studies consistently find that these practices, known collectively as alcohol screening, brief intervention, and referral to treatment, can be used effectively by providers across the health care spectrum to prevent or reduce alcohol misuse, as well as to identify other physical and mental health-related issues among their patients.[534] For example, the Alcohol as a Vital Sign initiative, a program operated through Kaiser Permanente, found that alcohol screening and brief intervention in

[528] Key Substance Use and Mental Health Indicators in the U.S.: Results from the 2023 National Survey on Drug Use and Health (https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annual-national.pdf)
[529] Farokhnia, M., et al. Mol Psychiatry. 2022 Nov;27(11):4642-4652. PMID 36123420.
[530] Chuong, V., et al. JCI Insight. 2023 Jun 22;8(12):e170671. PMID 37192005.
[531] Li, Y., et al. BMC Med. 2023 Nov 16;21(1):443. PMID 37968697.
[532] https://www.alchepnet.org/
[533] https://www.youtube.com/watch?v=mageIdGd_M4
[534] Chi, F. W., et al. BMJ Open. 2023 Jan 19;13(1):e064088. PMID 36657762.

primary care significantly improved drinking outcomes independent of AUD treatment, and that screening and brief intervention among patients with hypertension reduced both alcohol use and blood pressure. Additionally, in support of screening patients in primary care, NIAAA funded researchers recently demonstrated that the Alcohol Use Disorders Identification Test-Consumption, a key tool used by health professionals to screen people for alcohol misuse, had excellent test-retest reliability across various demographic groups and testing platforms, both in person and online.[535]

In another example of supporting primary care doctors and their patients, NIAAA launched the Healthcare Professional's Core Resource on Alcohol to assist clinicians in providing better care for patients whose alcohol use may be affecting their health. The resource consists of practical overviews of foundational knowledge to understand alcohol-related problems, the clinical impacts of alcohol, strategies for prevention and treatment of alcohol problems, and how to combine strategies and promote practice change.[536] The resource is a living document that is updated regularly, and it represents a major NIAAA effort in closing the gap between the number of people who need but do not receive treatment or help for alcohol-related problems.

To help adults who drink alcohol to better understand their relationship with alcohol, *Rethinking Drinking* was first issued in 2009 and has been NIAAA's most popular resource. In 2022, NIAAA published a major update and redesign of this popular booklet and website, *Rethinking Drinking: Alcohol and Your Health*.[537] This resource helps people take charge of their drinking with activities on handling urges to drink and building skills in refusing drinks. Rethinking Drinking also provides information on what counts as a "standard drink," interactive alcohol calorie and content calculators, short- and long-term consequences of alcohol misuse, signs and symptoms of AUD, resources for support, and more. Rethinking Drinking is complemented by the *Alcohol Treatment Navigator* website and the *Treatment for Alcohol Problems: Finding and Getting Help* booklet for people who might have AUD and need additional support.[538,539]

Early initiation of alcohol consumption increases the risk of a wide range of harmful consequences during adulthood, but especially during adolescence when brain development is still ongoing. A major priority within NIAAA's mission is research on the prevention and treatment of underage drinking and its harmful consequences. To raise awareness of and combat underage drinking, NIAAA launched the web resources, *NIAAA for Middle School and NIAAA for Teens*, in 2024.[540] NIAAA for Middle School contains interactive activities to help parents, caregivers, and teachers introduce and reinforce key messages about why early alcohol consumption is dangerous, what peer pressure is and skills to resist it, and other helpful resources on underage drinking. NIAAA for Teens is a research-based online resource aimed at preventing underage drinking by directly educating teens.[541] This web resource highlights how alcohol affects your body and mind, warning signs and symptoms of a problem with alcohol, and where to get help for alcohol-related

[535] Simon, C. B., et al. Alcohol Clin Exp Res (Hoboken). 2024 Feb;48(2):302-308. PMID 38099421.
[536] https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol
[537] https://rethinkingdrinking.niaaa.nih.gov/
[538] https://alcoholtreatment.niaaa.nih.gov/
[539] https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/treatment-alcohol-problems-finding-and-getting-help
[540] https://www.niaaa.nih.gov/alcohols-effects-health/niaaa-middle-school
[541] https://niaaaforteens.niaaa.nih.gov/

problems. These resources complement NIAAA efforts to create educational resources for middle school and teen audiences, including an NIH Kahoot! quiz collection on underage drinking released in 2024, and an award-winning virtual reality experience for teens about the effects of alcohol on the brain, which was released in 2023.[542]

Launched in FY12, NIAAA's National Consortium on Alcohol and Neurodevelopment in Adolescence-Adulthood is a multisite, longitudinal study to elucidate the effects of alcohol exposure on the developing adolescent brain into early adulthood, and to identify brain characteristics that may predict AUD and related problems. The five consortium sites enrolled more than 800 youth who were ages 12 to 21 at the start of the study and has maintained a 94 percent retention rate. Consortium researchers have shown that youth with a history of alcohol use exhibit weakened connections between brain networks involved in the regulation of emotional and cognitive functioning. More recent findings suggest that youth who have experienced childhood trauma have disrupted patterns of connections between brain networks that could predict future progression to AUD. Several consortium studies are helping to identify how the effects of stress alter adolescent and emerging adult mental health and substance use.

Tobacco and Nicotine Use

Tobacco use—particularly combustible tobacco—is among top causes of preventable death in the U.S.; and is associated with many diseases and conditions, including aortic aneurysm, asthma, cataracts (eye diseases), coronary heart disease, chronic obstructive pulmonary disease, many cancers, and stroke. According to the 2023 National Survey on Drug Use and Health, among Americans aged 12 or older in 2023, 22.7 percent (around 64.4 million people) used tobacco products or vaped nicotine in the past month, with the percentage being the highest among young adults aged 18 to 25 (30.0 percent or around 10.2 million people).[543] NIH supports research to prevent tobacco and nicotine use and treat the diseases and conditions that it causes. For example, NIDA-funded scientists recently developed a small molecule (SBI-0069330) drug treatment for nicotine use disorder that can be taken orally. It works by targeting a specific receptor found only in the brain and previously shown to play a role in depression as well as drug addiction. Completed in FY22, the study advanced through a full preclinical package and received IND approval from the FDA to begin Phase 1 clinical trials.[544] Researchers are also exploring the small molecule as a treatment for cocaine use disorder.

The Tobacco Regulatory Science Program is an interagency partnership between NIH—coordinated through ODP—and the FDA's Center for Tobacco Products to foster tobacco regulatory research. Through this partnership, NIH used FDA funds to award grants that can inform the Center for Tobacco Product's regulatory authorities.[545] The research funded through this partnership is intended to inform several FDA activities: product application review; scientific input to rules and regulations (e.g., product standards);

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[542] https://www.niaaa.nih.gov/alcohol-and-your-brain-virtual-reality-experience-0

[543] Key Substance Use and Mental Health Indicators in the U.S.: Results from the 2023 National Survey on Drug Use and Health (https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annual-national.pdf)

[544] https://clinicaltrials.gov/study/NCT04948827?tab=results

[545] https://prevention.nih.gov/tobacco-regulatory-research

compliance and enforcement; and public education.[546] Priority interest areas include research on: characterizing tobacco product composition and design; approaches that test the toxicity of tobacco smoke, aerosol, or specific constituents; effects of tobacco product characteristics on tobacco dependence and abuse liability; short- and long-term health effects of tobacco products; understanding knowledge, attitudes and behaviors related to tobacco product use; understanding how to effectively communicate the health effects of tobacco products; influences of tobacco marketing; and understanding of the impact of potential FDA regulatory actions.[547,548,549] Sixty-six new grants were funded through the partnership in FY22 to FY24.

The Tobacco Centers of Regulatory Science are the centerpiece of the on-going interagency Tobacco Regulatory Science Program partnership between NIH and FDA.[550] In 2022 the partnership solicited applications to fund the third round of the Regulatory Centers and seven research centers will receive, in total, approximately $140 million in funding from FY23 to FY27 (pending availability of funds). What scientists learn about tobacco through these research centers will help inform and assess FDA's ongoing and potential future regulatory activities. Center investigators have the flexibility and capacity to respond to FDA's research needs as issues are raised in today's rapidly evolving tobacco marketplace.

Through the Tobacco Regulatory Science Program, ODP and NCI worked with FDA to launch a new Center for Rapid Surveillance of Tobacco.[551] Through rapid surveillance and reporting of information, the center will enhance FDA's and the research community's ability to understand, document, and quantify changes in the tobacco product marketplace and tobacco use patterns. Research results from the center are expected to generate findings and data that are directly relevant in informing the FDA's regulation of the manufacture, distribution, and marketing of tobacco products to protect public health. In particular, the center will support more time-sensitive data collection, analysis, and reporting, making potentially actionable information available before more traditional data collection methods.[552]

In another joint initiative with FDA, ODP, and NCI, and also through the Tobacco Regulatory Science Program, research awards were made that aim to provide FDA with data to inform public education efforts on the continuum of risk for tobacco products. The continuum of risk is the understanding that the health risks for different tobacco products are not all the same and exist on a spectrum.[553] Specifically, the research will look at how FDA can accurately convey the relative risks of tobacco products to adults who use combustible tobacco, while ensuring these messages do not appeal to other audiences, including youth.

Medicinal Cannabis, Cannabidiol, and Psilocybin Research

[546] https://tobaccocontrol.bmj.com/content/31/Suppl_3
[547] Jabba, S. V., et al. Nicotine Tob Res. 2022 Jun 15;24(7):1037-1046. PMID 35167696.
[548] Rao, P., et al. Nicotine Tob Res. 2022 Jun 15;24(7):1055-1062. PMID 35100430.
[549] Foulds, J., et al. PLoS One. 2022 Nov 2;17(11):e0275522. PMID 36322562.
[550] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-004.html
[551] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-002.html
[552] https://tobaccocrst.org/
[553] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-23-021.html

Over the last decade or so, scientists have begun to explore the potential of developing therapeutics from compounds, many of them illicit substances, that are primarily used as recreational drugs. For example, researchers are testing 3,4-methylenedioxymethamphetamine, commonly known as ecstasy, and psilocybin, the active psychedelic compound in "magic mushrooms", as treatments for posttraumatic stress disorder in U.S. veterans.[554] The FDA has approved one plant-based cannabis drug called Epidiolex for treating seizures associated with two rare and severe forms of epilepsy as well as seizures associated with a rare genetic disorder called tuberous sclerosis complex. The FDA also approved two medicines (dronabinol and nabilone) that are made from a synthetic chemical that mimics the active ingredient in cannabis. They are used to treat nausea in patients with cancer who are having chemotherapy treatment, and to increase appetite in individuals with AIDS who do not feel like eating (wasting syndrome).[555]

Researchers, including those supported by NIDA and the NIH HEAL Initiative, are evaluating the therapeutic potential of cannabidiol as a medication for treating OUD and reducing relapse. Cannabidiol is one of around 113 identified cannabinoids in cannabis, along with tetrahydrocannabinol, the principal psychoactive constituent. Unlike tetrahydrocannabinol, cannabidiol by itself is not impairing, meaning it does not cause a "high". In September 2024, NIH-supported researchers developed an oral cannabidiol in a gelcap delivery system, and initial study results suggested it is safe, efficacious, and could be a viable non-addictive treatment for opioid craving and relapse prevention. As a result of these promising findings, the study successfully transitioned to a larger Phase 2 clinical trial.[556]

Researchers are also exploring psilocybin—a naturally occurring molecule found in more than 200 species of mushrooms and most known for its hallucinogenic effects—as a medication for treating OUD. In 2024, a NIDA-supported study used an innovative "seamless" adaptive design and an equally innovative treatment model to test the efficacy of psilocybin in OUD patients who continue to use non-prescribed opioids despite adherence to methadone treatment (a common medication for OUD). This well-powered efficacy trial has the potential to provide strong evidence and a practical treatment model for a full-scale drug development program to achieve an FDA indication for psilocybin as a treatment for OUD.

The Cannabis and Health Research Initiative, funded by NIDA, is establishing a national patient research registry, a cannabis product surveillance and testing program, a program to evaluate patient electronic medical records, and a data repository to integrate data from other sources with those collected as part of these initiatives.[557,558,559] The data collected and made available to researchers and the public will help inform clinical decision-making about the medicinal use of cannabis as well as help inform policy and regulatory decisions in the interest of public and patient health.

The Resource Center for Cannabis and Cannabinoid Research, funded by NIDA, NCCIH, NCI, and NIA, provides research tools to the scientific community that will allow advances in cannabis science through

[554] https://www.ptsd.va.gov/professional/treat/txessentials/psychedelics_assisted_therapy.asp
[555] https://www.cdc.gov/cannabis/about/index.html#cdc_disease_basics_risk-cannabis-as-medicine
[556] Humphreys, K., et al Lancet. 2022 Feb 5;399(10324):555-604. PMID 35122753.
[557] https://www.cannabisandhealth.org/
[558] Thrul, J., et al. Nat Med. 2024 Dec;30(12):3394-3395. PMID 39438664.
[559] Joo, J., et al. Internet Interv. 2024 Oct 26;38:100784. PMID 39611051.

both nonclinical and clinical studies.[560] The Center consists of three cores—research support, regulatory guidance, and research standards—that provide guidance through a centralized website as well as through workshops and webinars. The Center impacts a broad range of stakeholders, including the scientific community, federal and state agencies, institutional administrators, and suppliers of research materials.

Facilitating Research

Strengthening substance misuse and addiction research infrastructure and fostering its scientific workforce are essential for advancing preventive measures and treatments now and into the future. For example, NIDA's Avenir Award in Chemistry and Pharmacology of Substance Use Disorders supports early-stage investigators pursuing transformative research relevant to substance use disorders and addiction.[561] The awards promote the use of novel chemical and computational approaches for target identification and the application of emerging methods to discover new therapeutic options. Recent publications reflect cutting-edge work in molecular pharmacology, including applications in chemical neuroscience and diabetes.[562,563,564,565]

In addition to investing in research targeted towards specific drugs and SUDs, NIH also supports initiatives and programs to better understand the basic biology of addiction. NIDA's Single Cell Opioid Responses in the Context of HIV Program seeks to identify single cell transcriptomic and epigenetic changes associated with drug exposure and/or HIV infection.[566] Researchers in this program are assaying a variety of relevant brain regions in human post-mortem adult brain, macaques, rats, and mice. If fully successful, this work will lead to a much deeper understanding of the cellular and molecular mechanisms underlying addiction and the molecular effects of HIV infection/treatment in the CNS, and identify novel cellular and molecular therapeutic targets for the development of new addiction and/or CNS-specific HIV therapies.

NIDA's Animal Genetics Program aims to identify genetic, genomic, and epigenetic variants that underlie neural and behavioral processes and phenotypes relevant to SUD risk, trajectory, and comorbidities.[567] Research supported through the program will link genetic, genomic, and molecular mechanisms to neural circuit function and behavior and identify genomic and/or epigenomic variants that contribute to the genetic architecture of addiction, including single nucleotide variants, large and small structural variants, and mobile DNA. Researchers are encouraged to take genomics, multi-omics, and/or super intelligence/machine learning (SI/ML) approaches that integrate multi-level 'omics data, delineate gene networks, and/or uncover the function of known or newly discovered genetic or epigenetic variants. Studies supported through the program are expected to uncover novel mechanisms that contribute to

[560] https://r3cr.org/
[561] https://nida.nih.gov/about-nida/organization/divisions/division-neuroscience-behavior-dnb/chemistry-physiological-systems-research-branch-cpsrb/avenir-winners
[562] Brown, B. P., et al. J Chem Theory Comput. 2024 Feb 13;20(3):1434-1447. PMID 38215214.
[563] Bonifazi, A., et al. Diabetes. 2024 Sep 1;73(9):1411-1425.PMID 38869519.
[564] McCarroll, M. N., et al. ACS Chem Neurosci. 2024 Nov 20;15(22):4171-4184. PMID 39287508.
[565] Bagdasarian, et al. J Cereb Blood Flow Metab. 2025 May;45(5):908-919. PMID 39610321.
[566] https://nida.nih.gov/about-nida/organization/divisions/division-neuroscience-behavior-dnb/basic-research-hiv-substance-use-disorder/scorch-program
[567] https://grants.nih.gov/grants/guide/pa-files/PAR-24-269.html

various stages across the SUD trajectory and inform future studies about potential targets and therapeutic strategies for addiction.

NIDA's Human Genetics Program focuses on genetic determinants of vulnerability to drug use disorders and addiction, effects of addiction on epigenetic and non-coding factors that regulate gene expression, the consequences of exposure to addictive drugs at different windows of development, and new statistical methods for analyzing genetic and epigenetic data in humans. The identification of gene variants and epigenetic changes associated with addiction will identify drug targets for the treatment of addiction and lead to better understanding of gene environment interactions. Within this program, the NIDA Center for Genetic Studies produces, stores, and distributes clinical data and biomaterials (DNA samples and cell lines) and is an excellent resource for obtaining samples to make iPSCs from people with addictive disorders and for future whole genome sequencing studies and metabolomic studies.[568]

NIDA's NExUS Collaboratory on Neural Ensembles and Used Substances aims to gain actionable mechanistic insights into how drugs alter brain computations to promote behaviors and internal states that are characteristic of addiction, and to deliver harmonized data ecosystems for future applications of systems neuroscience approaches to SUD models.[569] Key to the success of the Collaboratory is the facilitation of team-science efforts encompassing multimodal data generation projects systematically profiling and producing spatially-resolved cell populations whose activity is tuned to tractable features of drug-associated experiences. Another key aspect is milestone-driven capacity building for data harmonization, analytics, sharing, and outreach.[570]

NIDA's Translating Socioenvironmental Influences on Neurocognitive Development and Addiction Risk initiative supports longitudinal research in animal models and advanced neuroscience and theoretical tools to elucidate mechanisms mediating the impact of the early-life social environment on neurobehavioral development and the risk for SUD and their comorbidities in adolescence and adulthood.[571] The initiative will also support generation of a data set for building computational models aimed at uncovering relationships linking early socioenvironmental conditions, neurocognitive developmental trajectories, and the emergence of SUD risk-relevant neurobehavioral phenotypes. If successful, it will help increase understanding of developmental windows that may be most sensitive to the effects of socioenvironmental factors and discover new potential neurobehavioral targets for interventions to prevent SUD.

The NIH HEAL Initiative funds a variety of networks and infrastructure efforts to coordinate and accelerate addiction research, with a focus on opioids, across institutions, communities, and disciplines. These efforts are designed to ensure that scientific advances translate quickly into practice. Through FY24, the NIH HEAL Initiative administered a research investment of approximately $3.9 billion, funded over 2,200 projects across 50 states and D.C., and supported more than 40 IND and device designations from the FDA to begin

[568] https://nidagenetics.org
[569] https://nida.nih.gov/about-nida/organization/divisions/division-neuroscience-behavior-dnb/basic-research-hiv-substance-use-disorder/nexus-collaboratory
[570] Chen, C., et al. Nature. 2024 Aug;632(8027):1092-1100. PMID 39048016.
[571] https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-25-037.html

human trials for novel treatments for pain, OUD, and overdose.[572] One of the ways HEAL is helping to speed scientific solutions to the opioid public health crisis is the HEAL Data Ecosystem, which aims to enhance progress and transparency by making HEAL-funded data accessible to all researchers.[573] This cloud-based platform includes over 60 de-identified datasets that users can explore to address new research questions. Another is the HEAL Data2Action program that focuses on leveraging real-time data to accelerate implementation of evidence-based interventions for OUD and pain management.[574]

THRO held Tribal Consultations in 2018 and 2022 to seek input on research needs for addressing opioid use and pain in Native communities.[575,576] In direct response to priorities identified, NIH launched the Native Collective Research Effort to Enhance Wellness Program to support Tribes and Native American Serving Organizations to conduct locally prioritized research to address overdose, substance use, and pain, including related factors such as mental health and wellness.[577] Research led by Native communities is essential for enhancing culturally grounded, strengths-based, effective, and sustainable intervention strategies. This collaborative partnership between NIH, Tribes and Native American Serving Organizations, and Ally Organizations is addressing the opioid and substance misuse public health emergencies in these communities.

Transplantation

More than six decades after the first successful kidney transplant ushered in the modern era of organ replacement therapy, transplantation now offers the only definitive treatment for end-stage failure of the kidney, liver, heart, lung, pancreas, and intestine. Yet the gap between need and supply remains stark: more than 103,000 Americans are on the national waiting list at any moment, and an average of 13 people die each day before a suitable organ becomes available.[578] Even so, 2024 marked a record 48,149 transplants—an unprecedented 3.3 percent year-over-year rise and the twelfth consecutive annual increase—highlighting steady growth in donor participation and surgical capacity.[579] Scientific advances in immunology, graft preservation, and regenerative medicine are gradually extending graft longevity and widening the donor pool, while other initiatives aim to ensure that historically underserved populations share in these gains. Regulatory science is also evolving: the FDA recently expanded tacrolimus (Prograf) to include prevention of lung-graft rejection, the first transplant-drug indication supported largely by real-world evidence and a sign of faster bench-to-bedside translation.[580] Together, these developments position the field to move beyond simple organ replacement toward durable immune tolerance and bio-engineered organs in the decade ahead. NIH supports basic, translational, and clinical research that

[572] https://heal.nih.gov/
[573] https://heal.nih.gov/data/heal-data-ecosystem
[574] https://www.hd2arasc.org/
[575] https://dpcpsi.nih.gov/thro/nih-tribal-consultation-opioid-crisis-indian-country
[576] https://dpcpsi.nih.gov/thro/tribal-consultations/nih-heal-initiative
[577] https://heal.nih.gov/research/research-to-practice/native-collective-research-effort-enhance-wellness-overdose-substance-mental-health-pain
[578] https://www.organdonor.gov/learn/organ-donation-statistics
[579] https://unos.org/media-resources/releases/u-s-surpassed-48000-organ-transplants-in-2024/
[580] https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

focuses on improving all aspects of transplantation, including research on the transfer of a solid organ, cells, tissues, or bone marrow; and research on the health and quality of life of transplant recipients.

Pig models, whose size and physiology closely mirror humans, are now indispensable for advancing biomedical research, including transplantation research; and they could become a new source of organs for the thousands of patients on the national transplant waiting list who die before receiving a transplant. ORIP's National Swine Resource and Research Center, co-funded by NHLBI and NIAID, has created genetically modified pig lines based on investigator-initiated requests that are advancing research and contributing towards new treatments and therapies for many diseases and conditions. The ORIP supported center supplies genetically modified pigs that recapitulate Alzheimer's disease, cystic fibrosis, retinal dystrophies, mitochondrial and DNA-repair disorders, pulmonary fibrosis, congenital heart anomalies, and phenylketonuria.[581] These pig models enable researchers to obtain more human-relevant and translatable results from their studies and develop drugs that are more likely to be effective in people.

The National Swine Resource and Research Center has contributed models to further enhance the compatibility of pig organs (kidney and heart) for transplantation studies. Using the same genome-engineering tools, the Center generates genetically modified "knockout" pigs, in which specific genes have been inactivated or "knocked out," to serve as transplantation donors. The genes are related to the production of molecules involved in the immune response and would trigger rejection of the pig organs by the recipient's immune system. The pigs are also genetically modified to express human genes to further enhance the compatibility of pig organs for transplantation. In a recent study, when Center "reference pigs" with a single gene knockout and single added human gene were compared to triple knockout pigs with seven added human genes, macaques that received kidneys from the more heavily genetically modified pigs, in combination with an immunosuppressive drug regime, showed significantly longer graft survival and reduced rejection compared to the reference pigs. However, when all immunosuppressive drugs were stopped, these recipients eventually rejected the grafts via antibody-mediated rejection, a rejection process where the body's own antibodies target the new organ as a threat.[582] Another Center pig line was used to demonstrate proof of principle of a procedure to deliver growing heart valve implants that would reduce the need for future re-operations in children. Results of the study, in which both donor and recipient were newborn piglets, were positive with good short-term survival.[583] Collectively, these ORIP-supported swine resources are accelerating transplantation research and furnishing versatile disease models that could reduce lifelong immunosuppression, shorten organ wait-lists, and advance treatments and therapies across organ systems and diseases.

The *HIV Organ Policy Equity Act* allows for the transplantation of organs from donors with HIV to recipients with HIV, aiming to increase the organ donor pool and improve outcomes for individuals living with HIV. Responding to the Act, NIAID-funded investigators led a prospective 26-center trial showing that kidneys from donors with HIV performed as well as those from donors without HIV in recipients with HIV. The one-year patient and graft survival was above 95 percent.[584] No excess opportunistic infections or virologic

[581] https://nsrrc.missouri.edu/
[582] Manook M, et al. Sci Transl Med 2024;16(751):eadk6152. PMID: 38865482.
[583] Medina CK, et al. Sci Rep 2024;14(1):12318. PMID: 38811656.
[584] Durand CM, et al. N Engl J Med 2024;391(15):1390-1401. PMID: 39413376.

failures were observed, confirming that donor HIV status alone does not compromise outcomes. These data provided the support for late-2024 rule changes that removed the requirement that HIV-positive to HIV-positive liver and kidney transplants be performed under IRB-approved research protocols and refined research criteria for heart, lung, and other HIV-positive to HIV-positive transplants.[585,586]

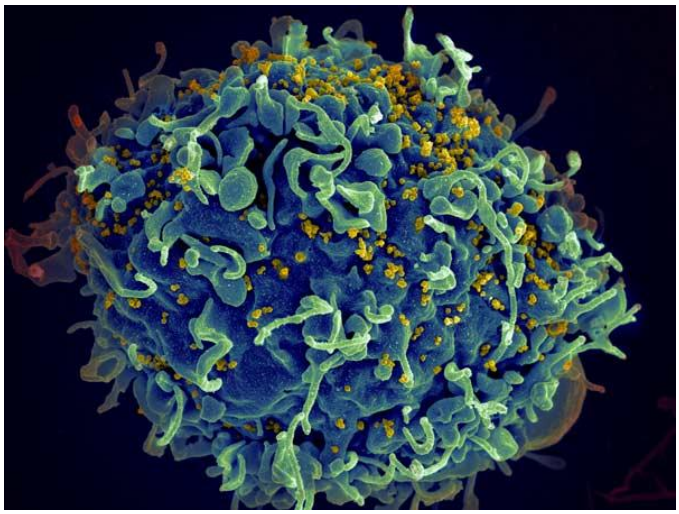


Figure 30. This human T cell (blue) is under attack by HIV (yellow), the virus that causes AIDS. The virus specifically targets T cells, which play a critical role in the body's immune response against invaders like bacteria and viruses. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, NIAID/NIH

One of the major reasons of failure following organ transplantation is rejection, which occurs when the recipient's immune system recognizes the transplanted organ as foreign and mounts an immune response against it. To address this, NEI-supported scientists developed a treatment where they take stem cells from a patient's own healthy eye, grow them in a lab, and transplant them onto the damaged cornea. In a Phase 1/2 trial of 14 participants with severe ocular-surface injury, 92 percent of participants achieved complete or partial success at 18 months, with corresponding gains in visual acuity. Because this therapy uses tissue taken from one part of a person's body and transplanted to another part of the same person's body, it avoids rejection. Another benefit is that it does not rely on scarce donor corneas, which may not always be easily obtainable. Successful translation of this regenerative approach could cut blindness-related costs and inspire similar patient-specific stem-cell therapies for other tissues.[587,588]

Urologic and Gynecologic Diseases and Conditions

Diseases and conditions affecting the bladder, lower urinary tract, and reproductive organs impose a significant health burden on individuals of all ages, often leading to substantial disability, reduced quality of life, and high health care costs. Among women in the U.S., gynecologic conditions such as uterine fibroids, endometriosis, ovarian cysts, and menstrual disorders, along with urologic diseases like kidney

[585] https://www.govinfo.gov/content/pkg/FR-2024-11-27/pdf/2024-27410.pdf
[586] https://www.govinfo.gov/content/pkg/FR-2024-12-30/pdf/2024-31265.pdf
[587] Jurkunas UV, et al. Nat Commun. 2025 Mar 4;16(1):1607. PMID: 40038272.
[588] https://www.nei.nih.gov/about/news-and-events/news/novel-stem-cell-therapy-repairs-irreversible-corneal-damage-clinical-trial

stones and urinary tract infections, are particularly prevalent and impactful. To address these widespread health challenges, NIH, led by NICHD and NIDDK, supports comprehensive research efforts. These efforts span the full spectrum of scientific inquiry—from understanding disease causes and progression to developing effective strategies for prevention, diagnosis, and treatment.

Prevalence, Risk Factors, and Underlying Biology

Lower urinary tract symptoms (LUTS), such as leaking urine, frequent urination, and getting up at night to urinate, are highly prevalent among women, yet women's bladder health has been understudied. To fill this gap, NIDDK supported the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium, a multi-center network of cross-disciplinary researchers from nine universities across the U.S.[589] PLUS aims to build the science to support prevention of LUTS in women and girls by advancing bladder health. In its early phases, PLUS developed novel measures of bladder health to complement existing measures of LUTS. In 2023, PLUS established the RISE FOR HEALTH study—a large, nationally representative cohort of community-based women to understand the spectrum of bladder health and prevalence of LUTS in the U.S., as well as individual, interpersonal, institutional, community, and societal factors that may contribute to bladder health and LUTS.

NIDDK is supporting many other initiatives to better understand LUTS and its underlying biology. One initiative is the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN). LURN was established to better understand the way these urinary symptoms show up in people, describe the impact and variability of symptoms, and to develop new patient-centric tools for improved measurement of clinical symptoms, all with the goals of informing future clinical studies and improving patient care.[590] LURN II, the second 5-year funding cycle of the network, led to increased, clinically useful understanding of subtypes of individuals with LUTS. For example, one finding suggests that two manifestations of overactive bladder—urinary urgency and urgency urinary incontinence—may reflect a spectrum of symptom severity rather than two distinct subtypes. Additionally, detailed urinary symptom questionnaires that were developed within the first phase of LURN have been integrated into clinical settings and made freely available on the LURN website, ensuring that these research tools are widely available for LUTS assessments in all communities.

Diagnosis, Treatment, and Prevention

NIH is also supporting innovative research to advance prevention, diagnosis, and treatment of urologic and gynecologic conditions. One such example is the persistent pain experienced by individuals with recurrent urinary tract infections (UTIs). UTIs can cause symptoms such as frequent urination and pain in the lower abdomen or while urinating. People who experience recurrent UTIs (two or more UTIs within six months of each other or three or more UTIs within a year) often continue to experience symptoms such as pain and increased urinary frequency even after the infection has cleared—a phenomenon that is not fully understood. Using a mouse model of recurrent UTIs, NIDDK-supported researchers found that increased nerve growth and sprouting in the bladder may be a major contributor to lasting pain symptoms

[589] https://plusconsortium.umn.edu/about-us
[590] https://nih-lurn.org/

experienced by people who experience recurrent UTIs. It could also explain why pain and voiding symptoms persist after an infection has been cleared.[591] This finding may help lead to new therapeutic approaches.

Researchers are also investigating how bacterial communities that form on urinary catheters may contribute to chronic or hard-to-treat infections, particularly in individuals who require long-term catheterization. While urinary catheters may be used for days or weeks during tissue healing after surgery or treatment, in some cases they are used long term and require periodic replacement, increasing the risk of infection. Catheter-associated UTIs are a common health care-associated infection and are responsible for increased morbidity and mortality, lengthened hospitalizations, greater costs, and antimicrobial use that can promote antibiotic resistance. In an NIDDK-supported study, researchers provided important insights toward better treatment strategies for catheter-associated UTIs by detailing the bacterial communities that form on long-term catheters.[592] Analysis of urine from people having their catheters replaced along with bacterial samples from the catheters revealed over 80 different bacterial species. Bacteria also persisted across multiple samplings over time despite a majority of patients receiving at least one course of antibiotics. These findings suggest that the polymicrobial nature of catheter microbial communities along with development of antibiotic resistance could contribute to the risk of UTIs in people using catheters long-term. Further characterization of the relationships among different bacterial species could provide key insights for determining which species to target for antimicrobial treatment of catheter-associated UTIs.

Beyond infections, other urologic concerns such as kidney stones are also receiving renewed attention, especially regarding strategies that could reduce recurrence and improve patient outcomes. Kidney stones are hard, pebble-like structures that form in the kidneys when a person has high levels of certain minerals in their urine. Some kidney stones may be able to pass through the urinary tract without treatment, while others can cause complications including severe pain, bloody urine, and UTIs. Asymptomatic kidney stones are more common than—and are often found alongside of—symptomatic stones, though there are conflicting views about the impact of leaving these asymptomatic stones behind during removal of symptomatic ones. An NIDDK-supported study in 73 people undergoing endoscopic surgery for removal of symptomatic kidney stones found that people had a lower chance of future kidney stone recurrence if smaller, asymptomatic kidney stones were removed alongside larger, symptomatic ones.[593] With further validation, these results could lead to new recommendations that may help reduce the risk of kidney stone recurrence.

A prevalent urologic issue in men—benign prostatic hyperplasia (BPH)—is being explored through multiple research avenues aimed at identifying new therapeutic targets to manage prostate enlargement and its effects on urination. The prostate, a small gland in the male reproductive system, commonly becomes enlarged with age. BPH is caused by the non-cancerous growth of the prostate due to increased reproduction of cells. This growth can squeeze the urethra and affect the flow of the urinary stream leading to changes or problems with urination. Two NIDDK-supported studies explored potential approaches for

[591] Hayes BW, et al. Sci Immunol. 2024 Mar;9(93):eadi5578. Epub 2024 Mar 1. PMID: 38427717.
[592] Nye TM, et al. Nat Commun. 2024 Jan 2;15(1):61. PMID: 38168042.
[593] Sorensen MD, et al. N Engl J Med. 2022 Aug 11;387(6):506-513. PMID: 35947709.

treating prostate enlargement. One study investigated a new potential target, soluble guanylate cyclase, which researchers found reduced prostate growth and helped restore urinary function in mice with BPH.[594] Another study, which assessed over 112,000 men, found that autoimmune disease-specific treatments, specifically tumor necrosis factor (TNF) inhibitors, may effectively treat or reduce the development of BPH by reducing cell multiplication and prostate inflammation (TNF is a chemical messenger produced by the immune system that induces inflammation).[595] Because TNF inhibitors can result in serious side effects, future studies to identify safer alternatives to reduce the inflammatory aspects of BPH will be important. If new treatments are shown to be safe and effective, individuals with BPH may one day have valuable alternatives to existing therapies.

In the area of gynecologic health, NIH is also working to address longstanding diagnostic delays, such as those faced by individuals with endometriosis—a common and often debilitating gynecological disease where tissue similar to the lining of the uterus grows in other places in the body, and that affects approximately 10 percent of women and girls worldwide. Launched in 2024, the RADx® Tech Advancing Cures and Therapies and Ending Endometriosis Diagnostic Delays Challenge offers up to $3 million in cash prizes to accelerate the development of innovative, non-invasive diagnostic technologies to improve diagnosis of endometriosis.[596] Novel approaches are urgently needed to identify those who are afflicted with the condition and to spur the development of new treatments and cures. The Challenge seeks to shorten the time to diagnosis, eliminate the invasiveness of current techniques, and/or improve accessibility, safety, convenience, and costs of diagnosis.

In parallel with efforts to improve diagnosis, researchers are also identifying new treatment options for endometriosis-related pain, including the repurposing of existing drugs that show promise in preclinical models. Fenoprofen, a nonsteroidal anti-inflammatory drug, successfully alleviated pain and inflammation in a rodent model of endometriosis.[597] Researchers chose the drug after using a computer algorithm to evaluate nearly 1,300 existing compounds for their ability to reverse gene expression related to endometriosis. The researchers observed that fenoprofen successfully alleviated vaginal hyperalgesia, a surrogate marker for endometriosis-related pain. Although fenoprofen belongs to a drug class that is one of the first-line treatments for endometriosis, analysis of electronic medical records from five healthcare institutions showed that the drug had been prescribed for less than one percent of patients with endometriosis or related conditions.

[594] Zabbarova IV, et al. J Pathol. 2022 Apr;256(4):442-454. Epub 2022 Feb 15. PMID: 34936088.
[595] Vickman RE, et al. Nat Commun. 2022 Apr 19;13(1):2133. PMID: 35440548.
[596] https://www.nichd.nih.gov/newsroom/news/081224-RADxTech-ACT-ENDO
[597] Oskotsky TT, et al. iScience. 2024 Mar 2;27(4):109388. PMID: 38510116.

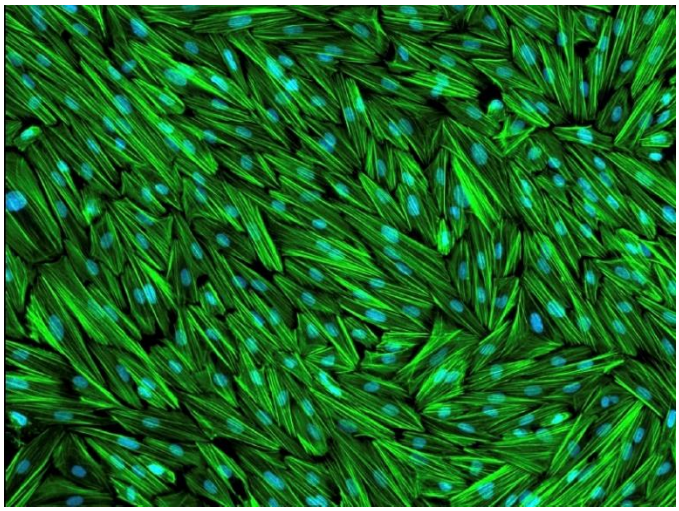


Figure 31. A tight-knit network of stromal cells from the human endometrium, the tissue that lines the inside of the uterus. The green strands represent a protein called filamentous actin, which helps the endometrium maintain its structure. The blue dots mark the endometrial cells' nuclei. Credit: Ryan Marquardt, Ph.D, DeMayo Lab, NIH

Complementing these pharmaceutical advances, novel, non-surgical methods such as nanoparticle-mediated therapies are being explored as less invasive alternatives to current endometriosis treatments. Endometriosis frequently causes debilitating pain and infertility, and treatments include hormone therapy and surgery to remove the patches of endometriosis tissue, both of which have unwanted side effects. Researchers are developing non-surgical approaches to remove endometriosis tissue. Their goal is to increase efficacy and ease of treatments while reducing the unwanted side effects of surgery. A research team adapted an experimental therapy called nanoparticle-mediated magnetic hyperthermia—a procedure that uses heat to remove cancerous tissues.[598] Using a mouse model of endometriosis, the researchers showed that this adapted technique may work as a treatment for endometriosis.

Similarly, for another common gynecologic condition—uterine fibroids—NICHD-supported research is exploring repurposed medications like tranilast to reduce tumor size, potentially offering new non-surgical treatment pathways for patients. Uterine fibroids, or leiomyomas, are tumors made of smooth muscle cells, fat cells, and fibroblasts, that grow in or on the wall of the uterus or womb. Previous studies have found that tranilast (a drug used to treat allergies and certain types of scars) slows the growth of fibroid cells in culture. Researchers implanted human fibroid tissue obtained from women following hysterectomies into mice and treated the animals with tranilast once a day for eight weeks.[599] They found that tranilast reduced the size of human fibroid tumors implanted in mice. These results warrant additional studies to evaluate this potential treatment for non-cancerous gynecologic tumors.

Although no temporary, reversable, oral contraception currently exists for men, researchers are making advances towards establishing a class of male conception pills. For instance, one NICHD-supported study explores an innovative, non-hormonal approach to male contraception that could provide a safe, on-

[598] Park Y, et al. Small. 2022 Jun;18(24):e2107808. Epub 2022 Apr 17. PMID: 35434932.
[599] Chuang TD, et al. Int J Mol Sci. 2023 Jun 21;24(13):10465. PMID: 37445642.

demand alternative to current methods. In a mouse study, researchers have identified a potential non-hormonal contraceptive that men could take shortly before sexual activity and have fertility restored the next day.[600] Researchers gave male mice a compound that temporarily disables soluble adenylyl cyclase, the enzyme essential for activating a sperm cell's ability to swim and mature so that it can travel through the female reproductive tract and fertilize an egg. In several tests, the researchers showed that the compound rendered mouse sperm cells immobile and prevented them from maturing. The compounds did not interfere with the animals' sexual functioning, wore off three hours later, and the males recovered their fertility. The researchers suggest that this work provides proof of concept that soluble adenylyl cyclase inhibitors have the potential to provide a safe, on-demand, non-hormonal, and reversible oral contraceptive for men.

Life Stages and Preserving Health Across the Lifespan

As humans age and proceed through each of the life stages, health risks, needs, and outcomes also evolve. NIH supports research dedicated to understanding the intricate dynamics between biological, psychosocial, and environmental factors on our health and well-being, from pre-birth to later in life. Research in these areas highlights NIHs' unique foci and expertise as well as the collaborative and complementary nature of their work. 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 supports research across the lifespan throughout each of the 27 ICs and many of the OD Offices. For example, NICHD—which focuses on the needs of children, mothers, 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 sheds light on the effects of earlier life experiences on health in the aging population. Research coordinated by ORWH in DPCPSI within the NIH OD, aims to improve research, treatments, and health for women. Through collaboration and co-funding, ICOs work together to improve the health and well-being of all Americans from conception to the final stages of life.

Prenatal and Maternal Health

Prenatal and maternal health is foundational to lifelong well-being, and NIH continues to support research to understand and improve outcomes for both mother and child. More than 90 percent of women take at least one medication during pregnancy and lactation. However, pregnant women and lactating women are often excluded from clinical research that could ultimately help these populations.[601] To address these issues, and as called for in the *21st Century Cures Act*, NICHD formed the Task Force on Research Specific to Pregnant Women and Lactating Women to advise the HHS Secretary regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women.[602] The Implementation

[600] Balbach M, et al. Nat Commun. 2023 Feb 14;14(1):637. PMID: 36788210.
[601] https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf
[602] https://www.nichd.nih.gov/about/advisory/PRGLAC

Working Group of Council hosted meetings on implementation activities beginning in 2023.[603] The group also held the inaugural stakeholder meeting for Prioritization of Therapeutic Research Needs for Pregnant, Postpartum, and Lactating Women to begin discussions on prioritization of drugs, vaccines, and dietary supplement research needs. The group released a report on implementation progress in 2024.

In another example of a long-term study assessing the effects of medications on pregnancy, NINDS-supported researchers studied the impacts of two common epilepsy medications, lamotrigine and levetiracetam, on children's neurological development.[604] They found that these medications did not affect neurological or verbal development, and that adequate folate supplementation during early pregnancy improved cognitive and behavioral outcomes. However, some antiseizure medications may affect fetal development differently, stressing the importance of balancing seizure control with minimizing fetal risks. These findings underscore the vital role of folate and provide guidance for managing epilepsy during pregnancy.

The complex interaction between fetal and maternal bloodstreams can help provide insight to scientists and clinicians into the health of a pregnancy. Noninvasive prenatal testing can be used to detect disorders and genetic characteristics of a fetus by drawing a sample of the mother's blood. In 2019, NHGRI and NICHD launched the Incidental Detection of Maternal Neoplasia Through Non-invasive Cell-Free DNA Analysis Study to explore how using these prenatal blood test results for a baby might also detect cancer in the mother.[605] The study is designed to gather evidence to guide further management of women with suspicious results, thereby addressing some of the current challenges faced by U.S. providers. The work highlights the importance of timely workup and management in pregnant women with such results, which provides the opportunity for early intervention and treatment. Another study, part of NICHD's Human Placenta Project, even showed that tiny, balloon-like particles released from the placenta into the maternal bloodstream could provide clues for identifying fetuses at risk for impaired growth.[606]

NHLBI funds multiple studies assessing the impact of cardiovascular conditions on pregnancy and effective interventions to prevent negative maternal and fetal health outcomes. For example, the Chronic Hypertension and Pregnancy trial aims to prevent adverse pregnancy and fetal growth outcomes due to mild chronic hypertension by focusing on interventions to safely control the condition during pregnancy. A recent study showed that treatment for mild chronic hypertension leads to better pregnancy outcomes and has no negative effect on fetal growth.[607] This discovery led to immediate changes in the American College of Obstetricians and Gynecologists' clinical practice guidelines for treatment of mild chronic hypertension during pregnancy. Another study highlighted that conditions such as obesity can greatly increase the chances of developing gestational hypertension, gestational diabetes, or preeclampsia and increased 30-year risk of cardiovascular disease.[608]

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[603] https://www.nichd.nih.gov/about/advisory/council/PRGLAC-implementation-WG-of-council
[604] Meador KJ, et al. JAMA Neurol. 2025 Jan 1;82(1):30-39. PMID: 39585668.
[605] https://www.genome.gov/Clinical-Research/Current-NHGRI-Clinical-Studies/IDENTIFY-Study
[606] Klemetti MM, et al. J Extracell Vesicles. 2024 Feb;13(2):e12413. Erratum in: J Extracell Vesicles. 2024 May;13(5):e12443. PMID: 38353485
[607] Tita AT, et al. N Engl J Med. 2022 May 12;386(19):1781-1792. Epub 2022 Apr 2. PMID: 35363951.
[608] Khan SS, et al. Circ Res. 2023 Oct 13;133(9):725-735. Epub 2023 Oct 10. PMID: 37814889.

Over 21,000 stillbirths occur in the U.S. each year. NIH formed the Stillbirth Working Group of Council[609] as a subgroup of NICHD's National Advisory Child Health and Human Development Council in response to an HHS request to lead a congressionally mandated task force. The group focused on known risk factors for stillbirths and communities at higher risk, the psychological impact and treatment for mothers following stillbirth, and current barriers to collecting data on U.S. stillbirth. The group released its report, *Working to Address the Tragedy of Stillbirth to HHS* in 2023, and in 2024, released a follow-up implementation recommendations report.[610] Additionally, to accelerate the development of fetal diagnostic and monitoring technologies, NICHD and NIBIB launched the Rapid Acceleration of Diagnostics (RADx®) Tech Fetal Monitoring Challenge—a multi-phase competition offering up to $2 million to scientists with the most innovative developments.[611] The competition aimed to advance accessible and cost-effective point-of-care and home-based devices that measure fetal health indicators to improve fetal health outcomes in low-resource settings. Top winners included a device to detect fetal stress, an SI model for early detection of congenital heart disease, and a wearable ultrasound patch to monitor fetal vascular health.[612]

Early inflammatory immune responses are linked to a higher risk of preterm birth and other complications. Because docosahexaenoic acid—an omega-3 fatty acid naturally found in certain seafood—has anti-inflammatory properties, scientists have investigated whether taking more than the 200 mg dose included in many prenatal vitamins helps reduce the probability of preterm delivery. A previous study found that pregnant women who took 1,000 mg/day had lower rates of preterm birth than those who took 200 mg/day. A new study offers a potential explanation for this effect by suggesting that a daily 1,000-mg dose of docosahexaenoic acid influences levels of two proteins that affect inflammatory immune responses that are linked to childbirth.[613]

The development of new tools to monitor the health of the placenta during pregnancy could be key to the prevention of issues during and after birth. In a recent study, NICHD funded researchers used a newly developed ultrasound technology capable of imaging microscopic blood vessels known as Super Micro-Vascular Imaging®.[614] Images and data are taken from the 12th through 37th week of pregnancy and provide a reference for normal placental development to help with comparison studies, tracking of placental development in healthy pregnancies, and identification of placental disorders that may lead to low birth weight, preterm birth, and other complications. In another study, researchers used single-cell RNA sequencing of the placenta and its surrounding membranes to understand the communication that occurs between maternal and fetal cells during labor.[615] Researchers have also used this technique in animal models such as zebrafish to develop a genetic atlas of human development.[616] The continued

[609] https://www.nichd.nih.gov/about/advisory/council/stillbirth-working-group-of-council
[610] https://www.nichd.nih.gov/sites/default/files/inline-files/NICHD_Stillbirth_WG_Report_July_2024_508.pdf
[611] https://www.challenge.gov/?challenge=radx-tech-fetal-monitoring
[612] https://www.challenge.gov/?challenge=radx-tech-fetal-monitoring&tab=winners
[613] Valentine CJ, et al. Nutrients. 2021 Nov 26;13(12):4248. PMID: 34959801
[614] Horgan R, et al. Ultrasound Obstet Gynecol. 2023 Dec;62(6):860-866. PMID: 37470712.
[615] Garcia-Flores V, et al. Sci Transl Med. 2024 Jan 10;16(729):eadh8335. Epub 2024 Jan 10. PMID: 38198568.
[616] Sur A, et al. Dev Cell. 2023 Dec 18;58(24):3028-3047.e12. Epub 2023 Nov 22. PMID: 37995681.

development of this method could help better understand what allows for typical labor and the causes of preterm labor and delivery in humans.

Sepsis, a life-threatening complication of bacterial and other infections, is a leading cause of maternal and newborn deaths worldwide, especially in low- and middle-income countries. Azithromycin, an inexpensive antibiotic effective against a broad range of bacteria, is known to reduce maternal infection when given intravenously during cesarean delivery. Results from the NICHD funded A-PLUS trial, which included more than 29,000 women in seven low- and middle-income countries, showed that a single oral dose of the antibiotic azithromycin can reduce the risk of postpartum sepsis and death among women who deliver vaginally by one-third.[617] Azithromycin did not reduce the risk of stillbirth, newborn sepsis, or newborn death. These results could help save the lives of women during childbirth everywhere.

Maternal morbidity refers to any condition or health complication experienced by a woman during pregnancy, which can have short- and long-term effects, especially when severe. With involvement form several ICOs, NIH launched the Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) initiative in 2019 in response to high rates of pregnancy-related complications and deaths in the U.S. The IMPROVE initiative supports research to reduce preventable causes of maternal deaths and improve health for women before, during, and after pregnancy. It includes a special emphasis on populations that are disproportionately affected. In FY22, NIH launched a $3 million challenge competition to encourage U.S. community-based and advocacy organizations to develop the infrastructure and capabilities necessary to conduct maternal health research. The IMPROVE Connecting the Community for Maternal Health Challenge supports community-based organizations and provides them with the tools and support (training, mentorship, research resources, and cash awards) necessary to engage in impactful maternal health research and to increase competitiveness in pursuit of federal funding opportunities.[618] In FY23, NIH established Maternal Health Research Centers of Excellence to develop and evaluate innovative approaches to reduce pregnancy-related complications and deaths and promote maternal health for all.[619] This includes support for a project scientist to provide continuous subject matter expertise and guidance to advance research activities and project implementation in individual centers of excellence.

[617] Tita ATN, et al. N Engl J Med. 2023 Mar 30;388(13):1161-1170. Epub 2023 Feb 9. PMID: 36757318.
[618] https://www.nichd.nih.gov/research/supported/challenges/community-maternal-health
[619] https://www.nih.gov/news-events/news-releases/nih-establishes-maternal-health-research-centers-excellence



Figure 32. Reproduction is a highly complex process that packages parents DNA into egg and sperm cells, to be passed along to their children. This intricate process, which involves a particular subset of genes, sometimes fails and leads to infertility. Credit: Ernesto del Aguila III, NHGRI/NIH

Effects of maternal morbidity can be even more impactful for individuals of specific demographic groups, as shown by recent studies led by NIMHD. One recent study examined the associations between hospital visits before and during pregnancy and severe maternal morbidity at delivery.[620] Researchers found a strong association between previous nonbirth hospitalizations and the likelihood of severe maternal morbidity at delivery. Severe maternal morbidity was more prevalent among women older than 40 years of age, Black or African American women, and women with chronic and obstetrical comorbidities. The findings highlighted the need for more research on early identification of high-risk cases and prevention of severe maternal morbidity. Another study revealed that Black or African American mothers and infants fared the worst in terms of mortality rates. The researchers highlight the need for more research on the effectiveness of programs aimed to mitigate these disparities.

Disparities in risks to health and life can even continue after delivery for many mothers in the U.S. One study examined the death certificates of mothers from 33 states and Washington D.C., over the period of a decade, and found that 20 percent of deaths during pregnancy and the first year after childbirth are due to drug use, suicide, and homicide.[621] Drug-related deaths nearly tripled between 2010 and 2019. There were disproportionately high rates of homicide for Black or African American women, and much higher rates of suicide for AI/AN women. The findings suggest the need for research to identify risk factors and prevention approaches, underscore the need to address racial and ethnic disparities in these deaths, and call for attention to barriers to accessing care and support. To begin to address this need, NIH, led by THRO, participated in Tribal consultations for NIH's IMPROVE Initiative.[622] These consultations aimed to better

[620] Meadows AR, et al. Am J Obstet Gynecol MFM. 2023 Jul;5(7):101014. Epub 2023 May 12. PMID: 37178717.
[621] Margerison CE, et al. Obstet Gynecol. 2022 Feb 1;139(2):172-180. PMID: 34991132.
[622] https://dpcpsi.nih.gov/thro/tribal-consultations/nih-improve-initiative-maternal-health-research-centers-of-excellence

understand how to launch and encourage applications to propose Native-focused research centers led by American Indians and Alaska Natives.

The postpartum period can be a sensitive time for women who have given birth for mental and physical health risks. In FY24, The Pathways to Prevention workshop, *Identifying Risks and Interventions to Optimize Postpartum Health,* aimed to address the maternal health crisis by identifying and closing research gaps in postpartum health.[623] To organize the workshop, ORWH partnered with NHLBI, NICHD, NIMHD, and ODP in DPCPSI within the NIH OD. The workshop emphasized how factors such as differences in local infrastructure and access to care increase African American and AI/AN women's risk of postpartum morbidity and mortality. To further address issues such as these, NIH launched the RADx® Tech Maternal Health Challenge, an $8 million prize competition to encourage development of maternal health diagnostics for postpartum women, focused on use in regions that have limited access to maternity care.[624] The eight winning teams developed home-based and point-of-care diagnostics, including wearables and other accessible technologies to improve postpartum health outcomes. The first six weeks postpartum are when most maternal deaths occur and the RADx® Maternal Health program developed technologies for use during this period and up to one year after delivery or the end of a pregnancy.[625]

Studying maternal health and the process of pregnancy could also help build understanding of conditions and treatments for other stages of life. Calcium demand for milk production and the postpartum drop in estrogen has been known to trigger significant maternal bone loss. NIA-funded investigators identified a female-specific hormone, called cellular communication network factor 3, that is secreted by the brain and acts to restore bone mass during lactation in mice.[626] They found that when this hormone is administered to males or females, bone mass is increased in both sexes. These findings may lead to new treatments for osteoporosis in both men and women. To discuss the impacts of pregnancy on aging, NIA, NICHD, and ORWH hosted the *Long-Term Effects of Pregnancy on Aging* workshop.[627] This workshop examined the major research gaps and opportunities on the enduring effects of pregnancy on the health of women who have previously given birth. Topics discussed included the costs of reproduction on aging, how pregnancy affects the hallmarks and metrics of aging, and late effects of pregnancy complications.

Infancy to Adolescence

Infancy through adolescence marks a transformative period for growth and development that can affect the rest of a person's life. NIH has a robust biomedical and behavioral research portfolio designed to shed light on the biological, environmental, and other factors shaping health across these stages as well as advancing interventions designed to maximize transition through this life stage. NIH has been conducting multiple large, national, and long-term studies dedicated to gaining a better understanding of a variety of health factors affecting infants and children. The Healthy Brain and Child Development Study, supported by NIDA, is the largest long-term study of early brain and child development in the U.S. The study is

[623] https://orwh.od.nih.gov/in-the-spotlight/all-articles/pathways-to-prevention-p2ps-postpartum-health-initiative
[624] https://www.nichd.nih.gov/newsroom/news/091522-RADxTech
[625] https://www.nichd.nih.gov/newsroom/news/101524-RadxTech-Maternal-Health-Winners
[626] Babey ME, et al. Nature. 2024 Aug;632(8024):357-365. Epub 2024 Jul 10. PMID: 38987585.
[627] https://www.nia.nih.gov/research/dab/workshops/workshop-long-term-effects-pregnancy-aging

collecting information from a cohort of pregnant women before birth and from their infants beginning at birth, and it will continue collecting information from the caregiver and child through early childhood. Approximately half the sample will include pregnant women who experience adversities during pregnancy, including, but not limited to, exposures to substances. The Adolescent Brain Cognitive Development Study, also supported by NIDA, is a landmark study of adolescent brain development conducted by a Coordinating Center; a Data Analysis, Informatics, and Resource Center; and 21 research sites across the U.S.[628] Researchers track the biological and behavioral development of children starting at ages 9-10 and into young adulthood. Data Release 5.0,[629] released in FY23, contains early longitudinal data on the full participant cohort, including 2-year follow-up neuroimaging data, as well as phenotypic data through the 3-year follow-up visits.

NIH's *All of Us* Research Program, initially focused on adults, is building the infrastructure to expand discovery to children.[630] While the program already collects longitudinal electronic health records, including pediatric data from over 40,000 adult participants with whole genome sequences, it took a major step forward in August 2024 by launching a pediatric enrollment pilot. By September 2024, five sites had initiated pilot programs to test protocols for enrolling children ages 0-6. These efforts lay the groundwork for broader pediatric participation, ensuring the program is ready to scale once funding becomes available.

NICHD is committed to newborn screening research, with the goal of detecting conditions early enough to intervene and prevent symptoms from developing. To achieve this goal, the Institute's research portfolio includes studies to improve existing and develop new screening methods and novel screening technologies, as well as to find innovative therapies for detectable disorders.[631] Because many of the conditions detected by newborn screening can cause intellectual and developmental disabilities if not treated, a lot of the newborn screening research activities are supported through the Intellectual and Developmental Disabilities Branch.[632] These include the *Hunter Kelly Newborn Screening Research Program*, which focuses on identifying, developing, and testing new newborn screening technologies in order to improve existing tests and develop new tests; and developing and testing innovative interventions and treatments for conditions that can be detected through screening but which are not yet treatable, and evaluating and improving treatments and strategies for disorders with existing treatments.

One of the hallmarks of infancy is the development of speech. Researchers from the NIH Common Fund High-Risk, High-Reward Research program discovered a link between how words sound and infant speech development.[633] They investigated which acoustic properties had the most impact on the way infants learn to say words for the first time. They found that infants were more likely to say words earlier in their speech development if words were repeated often and with greater sound variation. These studies help us

[628] https://abcdstudy.org/about/
[629] https://nida.nih.gov/research-topics/adolescent-brain/longitudinal-study-adolescent-brain-cognitive-development-abcd-study/abcd-curated-data-releases
[630] https://allofus.nih.gov/article/announcement-nihs-all-us-research-program-begins-limited-enrollment-children
[631] https://www.nichd.nih.gov/health/topics/newborn/researchinfo/activities
[632] https://www.nichd.nih.gov/about/org/der/branches/iddb
[633] Bulgarelli F, et al. Dev Sci. 2024 Nov;27(6):e13545. Epub 2024 Jul 8. PMID: 38978148.

understand how infants learn to understand words and shed light on human speech development processes.

NIH seeks to build evidence for the safest and most effective treatments and drug therapies for infants and children experiencing infections or conditions. Labels for the antifungal drug fluconazole now include information about its recommended usage and dosage in infants, including those born prematurely, informed by data from research funded by NICHD.[634] Fluconazole is prescribed to prevent and treat fungal infections, and often used to treat infants with candidiasis, an infection caused by Candida yeast. Babies born prematurely or at very low birthweight are particularly susceptible to bloodstream infections with Candida. Yet previous fluconazole labels contained extremely limited information about how to use the drug in infants. The newly revised drug labels include information about how fluconazole is distributed, metabolized, and cleared in newborns and older infants and provide dosing suggestions.

Engaging communities with families who experience the most health risk factors is an important tool for prevention of long-term diseases and conditions. Launched in 2022, the Early Intervention to Promote Cardiovascular Health of Mothers and Children program, led by NHLBI, promotes cardiovascular health in mothers and children up to five years old.[635] The initiative is a partnership with other HHS divisions, like the Health Resources and Services Administration and the Administration for Children and Families, and certified local home visiting programs. The program works directly with communities that have a high burden of cardiovascular disease. It includes seven clinical centers around the country that are investigating ways to lower the incidence of cardiovascular risk factors, including obesity, hypertension, diabetes, and social determinants of health.

Despite many efforts, the development of medical devices for children continues to lag far behind that for adults. As a result, children may have no devices that meet their needs, or they may be offered use of a medical device designed for adults despite a lack of robust scientific evidence of its safety and effectiveness for children. To address this, NIH launched a public-private partnership to advance pediatric medical device development.[636] Led by NICHD and NIBIB, NIH and partners, including the Foundation for NIH, have developed a detailed plan to build and launch a partnership that will bring together the resources of U.S. government agencies and private sector organizations, including industry and non-profits.

For the past few decades, NIH has funded research on the prevalence, causes, and consequences of child abuse and neglect. Bruising on a young child is often dismissed as an accidental injury but, depending on its location and other characteristics, it can be an early sign of physical abuse. A new smartphone app, developed by NICHD funded researchers, may improve early recognition of physical child abuse.[637] By applying an evidence-based strategy, the app can help healthcare providers and social workers evaluate bruising on children younger than four years of age and identify cases that may need further investigation for child abuse.

[634] https://www.nichd.nih.gov/newsroom/news/031224-fluconazole-labeling-updates
[635] https://hvenrich.org/ENRICH_Main.asp
[636] https://www.nichd.nih.gov/newsroom/news/092623-pediatric-medical-device-development
[637] https://www.nichd.nih.gov/newsroom/news/060823-LCAST

In this increasingly digital world, NIH strives to better understand how technology and media affect development, health outcomes, and interpersonal relationships. In 2021, NICHD announced a funding solicitation for research projects to examine how digital media exposure and use impact developmental trajectories and health outcomes in early childhood or adolescence.[638] These efforts will help advance progress toward the goal of discovering how technology exposure and media use affect developmental trajectories, health outcomes, and parent-child interactions.

Adulthood

Adulthood encompasses the longest phase of the human lifespan. NIH-supports research during this life stage that will help to sustain health, manage disease risk, and promote quality of life across the American population. Furthermore, health trajectories during adulthood can differ between men and women, reflecting both biological and social influences. This makes it important to take these distinctions into account, ensuring that advances in prevention, diagnosis, and treatment are responsive to everyone's needs. 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. ORWH coordinates and leads much of this research across NIH, including the development of the 2024-2028 NIH-Wide Strategic Plan for Research on the Health of Women, prioritizing broad aspects of women's health research to be addressed over this five-year period.[639] Subsequently, every two years, ORWH publishes the *Report of the Advisory Committee on Research on Women's Health*. Required by the *NIH Revitalization Act of 1993*, the eighth biennial report on NIH's women's health research covers FY21 and FY22.[640] These reports serve as an important resource for Congress, the scientific community, and the public.

NIH also supports health issues and conditions that are male-specific or that affect men differently than women. For example, Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a severe autoinflammatory disease primarily affecting males and involving episodes of fever, abnormal inflammation, and debilitating symptoms. VEXAS is caused by mutations in the *UBA1* gene. NIAMS intramural researchers analyzed RNA levels in individual bone marrow cells from men with VEXAS syndrome and found both hyperinflammation and dominance of certain immune subtypes in the blood stem cells with *UBA1* mutations.[641] Although the mechanisms underlying VEXAS are still not fully understood, this finding provides insights that could be useful for future efforts to develop therapies.

To address disproportionately high rates of stroke and dementia among men, the NINDS public health information campaign Mind Your Risks® was launched using bold messaging to communicate that high blood pressure increases the risk for stroke and cognitive impairment and dementia later in life.[642] The campaign was based on growing evidence from NIH-supported research linking cardiovascular risk factors to brain health, and the campaign's updated messages specifically aim to engage young and middle-aged men from subpopulations on the importance of controlling their blood pressure. The campaign also

[638] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-009.html
[639] https://orwh.od.nih.gov/about/strategic-plan
[640] https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Biennial%20Report_121823_1516_F_508c_Optimized.pdf
[641] Wu Z, et al. Cell Rep Med. 2023 Aug 15;4(8):101160. PMID: 37586319.
[642] https://www.ninds.nih.gov/health-information/public-education/mind-your-risks

includes ready-to-use resources that are designed for healthcare providers, educators, and community leaders—but they are also available to anyone looking to raise awareness about dementia and high blood pressure in their communities.

NIH is committed to advancing our understanding of both biological processes underlying conditions disproportionately affecting women and tools/methods development that provide the foundation for improvements in diagnosis and treatment of such conditions. NIGMS has led multiple efforts to work toward this advancement, including releasing a solicitation in FY22 for administrative supplements for research on women's health in Institutional Development Award (IDeA) States.[643] In June 2024, NIGMS and ORWH co-hosted the 1st *NIH Symposium on Women's Health Research in the IDeA States* for awardees of these supplements.[644] And in FY23, NIGMS and ORWH released a notice announcing interest in supporting women's health research in IDeA-eligible states through the Centers of Biomedical Research Excellence program.[645]

Despite many significant advances in diagnosis and treatment, HIV continues to significantly affect thousands of American women each year. ORWH partners with OAR, in DPCPSI within the NIH OD, to coordinate the NIH-wide HIV and Women Working Group.[646] This internal, NIH-wide committee convenes NIH staff with expertise in women's health and/or HIV to provide recommendations on programmatic and scientific focus areas and action plans that leverage ongoing NIH investments at the intersection of women's health and HIV. OAR and ORWH also launched the HIV and Women Signature Program in 2023 to address the unique needs of women and girls who are disproportionately affected by HIV. The program has produced multiple funding opportunities co-sponsored by different ICs to address critical research gaps and priorities. In 2024, OAR and ORWH organized a two-day scientific workshop comprising of more than 700 participants to review the state of the science on HIV and women and set the future research agenda.

In 2024, NIH was part of a Federal Focus on Women's Health Research to expand and improve research on women's health, and to prioritize federal investments in women's health research.[647] NIH was called to maximize the impact of women's health research, address the needs of women across the life course, accelerate small business and technology research and development in women's health, and advance the study of women's health through research and data standards. Multiple ICOs contributed to the efforts to address these challenges.

ORIP's Shared Instrumentation Program funds the acquisitions of a wide spectrum of commercially available scientific instruments that are critical to the conduct of cutting-edge research in all scientific disciplines, including women's health. For example, women's health research supported by the program generated at least 1,032 publications during FY22-24 ranging from understanding of zygotic genome

[643] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-22-005.html
[644] https://orwh.od.nih.gov/womens-health-research-in-institutional-development-award-idea-programs#card-1588
[645] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-23-012.html
[646] https://oar.nih.gov/women
[647] https://orwh.od.nih.gov/archive/federal-focus-on-womens-health-research

functions, to studying preeclampsia and gestational hypertension during pregnancy, and to clinical treatment of ovarian and breast cancers.

To contribute to the advancement the study of women's health through research and data standards, ORWH sponsors the Specialized Centers of Research Excellence on Sex Differences.[648] The Centers are focused on translational research at multiple levels of analysis to identify the role of biological sex differences on the health of women; training and education; dissemination of innovative, sex-based, and informed translational research methods and best practices; and leadership in the development and promotion of standards and policies for the consideration of sex differences in biomedical research. Since 2019, ORWH has sponsored the NIH Junior Scholar Travel Awards program which provides funds for junior investigators selected to attend the Organization for the Study of Sex Differences annual meeting, present their research, and network with leading scientists and clinicians working to advance research on sex differences.

NIH supports many other and varied approaches for advancing the health of women. In FY24, the Pathways to Prevention Program, led by ODP in partnership with ORWH, spearheaded efforts to undertake a systematic evidence review on the use and efficacy of treatments for symptoms arising during the menopausal transition.[649] In 2024 a new program sponsored by ORWH provided funding for two junior investigators for registration and travel to the main program of the 2024 Annual Meeting of the Menopause Society.[650] To accelerate technological innovation and translate scientific discoveries into health improvements for women, ORWH participates in multiple funding solicitations through the Small Business Education and Entrepreneurial Development Office. This participation emphasizes the key role that small businesses play in advancing innovation in women's health.[651]

Aging

Aging represents a complex biological and social transition that involves changes in physical health, cognitive function, and social roles, affecting both individuals and society at large. As the age distribution of the U.S. shifts towards more older Americans, scientists are studying diseases and conditions experienced in older age, as well as studying prevention methods that promote healthy aging. In recent years, research has identified several hallmarks of aging that represent distinct molecular and cellular mechanisms of aging. They include: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis (healthy balance and quality of its proteins), deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.[652] In 2023, NIA issued three funding opportunities to encourage innovative research on the interactions that

[648] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-014.html
[649] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention
[650] https://menopause.org/annual-meetings/menopause-society-annual-meeting-2024/awards-and-prizes
[651] https://orwh.od.nih.gov/innovation-in-womens-health-research-at-nih#card-1650
[652] López-Otín C, et al. Cell. 2013 Jun 6;153(6):1194-217. PMID: 23746838.

occur between the hallmarks of aging.[653,654] These interconnected funding opportunities resulted in 26 funded research projects. NIA also established a consortium for the grantees to share their research findings, generate new collaborations, and promote tools and technology development.

Although all people who live a full life will experience some of these hallmarks of growing older, aging is a complex biological phenomenon with remarkable individual and population variation. NIA hosted two workshops to explore this topic in more depth—the first in June 2023, examined how determinants of prolonged health can be identified by investigating heterogeneity. In June 2024, the follow-up workshop focused on translating research findings on heterogeneity into improved health. The workshops provided a venue for researchers to discuss challenges and opportunities in aging biology to fuel future research funding opportunities.

One specific hallmark of aging that scientists seek to better understand is cellular senescence. This phenomenon occurs when cells stop replicating but are still metabolically active and can release molecules that affect other cells, sometimes negatively. Researchers from the Cellular Senescence Network program, funded by the NIH Common Fund, showed that during aging, senescent cells accumulate in the skin, which may lead to senescence in other organs, such as muscles and the brain.[655] This discovery supports the concept that senescent cells in the skin could drive broader, systemic aging. To expand on these findings, researchers funded by NIA explored how senescence affects physical performance abilities.[656,657] Study results showed that levels of cellular senescence were associated with the onset of major mobility disability and with levels of physical activity. This decline in mobility is important as physical activity can often reduce or reverse senescence's deleterious effects on mobility as shown by another pair of recent NIA and NCATS-funded studies.[658,659] These studies also highlighted that preservation of muscle mass may predict responsiveness to physical activity interventions targeting impairments in multiple functional domains in this population; thus, informing selection of patients who are the best candidates for such interventions.

Much of research that focuses on older age aims to understand the causes, mechanisms, and treatments for disorders of older age, such as dementia or cognitive impairment. NIH funds the Aging and Cognitive Health Evaluation in Elders Study, a multicenter, randomized control clinical trial aiming to determine if treating hearing loss in older adults reduces cognitive decline over a three-year period.[660] A primary analysis showed no difference in the rate of change in cognitive functioning between people who received the hearing aids and those who did not. However, a subgroup analysis demonstrated that participants with

[653] https://www.nia.nih.gov/research/blog/2022/03/three-interconnected-foas-encourage-fresh-look-aging-hallmarks
[654] https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-23-012.html; https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-23-013.html; https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-23-015.html
[655] Franco AC, et al. Aging Cell. 2025 Jan;24(1):e14340. Epub 2024 Oct 7. PMID: 39374134.
[656] Fielding RA, et al. Geroscience. 2022 Dec;44(6):2757-2770. Epub 2022 Nov 11. PMID: 36367600.
[657] Fielding RA, et al. J Gerontol A Biol Sci Med Sci. 2024 Mar 1;79(3):glad257. PMID: 37948612.
[658] Custodero C, et al. J Am Med Dir Assoc. 2023 Apr;24(4):489-496. Epub 2023 Mar 3. PMID: 36878264.
[659] Pandey A, et al. JAMA Cardiol. 2023 Feb 1;8(2):167-176. PMID: 36598761.
[660] https://www.achievestudy.org/about

a higher risk of dementia had an almost 50 percent reduction in the rate of cognitive decline among the people who received hearing aids compared to those people without risk of cognitive decline.[661]

Older adults with dementia often experience simultaneous cognitive and mobility decline, compounding challenges for these individuals and their caregivers. Some individuals with dementia who need assistance with daily activities often prefer to seek care within their home or a community setting. In FY23, NIA funded the Community Care Network for Dementia to promote greater understanding of dementia home- and community-based services.[662] The network is focused on fostering collaborations within the dementia community; developing new data tools to analyze structure, processes, and outcome measures of dementia services; and supporting mentorship programs to cultivate a stronger home- and community-based services research community. NIA also convened the *2023 Dementia Care and Caregiving Research Summit*.[663] Attendees of the summit reviewed research progress, highlighted innovative and promising research, and identified remaining unmet research needs with input from the research community, persons living with dementia and their care partners, as well as healthcare providers.

Individuals living with dementia who also come from populations that experience health disparities may especially benefit from initiatives focusing on quality care. NIMHD and other ICs launched the Advancing Health Care for Older Adults from Populations That Experience Health Disparities initiative in FY22.[664] Research funded under this initiative will work towards improving diagnostic and clinical care guidelines, encouraging shared decision-making between clinicians and care teams to enhance care planning and patient agency, and developing effective strategies for coordinating care for older adults. The importance of this work is emphasized by the recent finding that low educational attainment in high school can predict more declines in cognitive ability and risk for dementia, which could further exacerbate disparities.[665]

Negative effects of aging are even greater for those dealing with chronic disorders or diseases, such as HIV. In 2022, OAR launched the HIV and Aging Signature Program to strengthen the science of HIV-related co-occurring conditions among people aging with HIV.[666] Over half of individuals with HIV in the U.S. are aged 50 or older and are developing chronic diseases (e.g., cardiovascular illness, neurocognitive decline, cancer) at earlier ages and at a more accelerated rate than people without HIV. OAR sponsored two virtual workshops and a panel discussion in September 2023 and October 2024 highlighting the importance of innovative care models and ongoing mentorship for early career investigators. OAR facilitated collaborations across several federal agencies and community groups to address the complex needs of older adults and long-term survivors with HIV. Multiple funding opportunities in HIV and aging emerged from these activities with co-sponsorship by 15 ICs. OAR also convened a working group co-led by NIA to link NIH, people aging with HIV and their community advocates, researchers, and relevant U.S. government agency partners in discussions to foster collaboration, identify research gaps and opportunities, facilitate integrative research and training, and promote faster implementation of research results.

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[661] Lin FR, et al. Lancet. 2023 Sep 2;402(10404):786-797. Epub 2023 Jul 18. PMID: 37478886.
[662] https://sph.emory.edu/can-d/
[663] https://www.nia.nih.gov/2023-dementia-care-summit
[664] https://grants.nih.gov/grants/guide/pa-files/PAR-24-273.html
[665] Huh J, et al. Alzheimers Dement. 2024 Apr;20(4):2662-2669. Epub 2024 Feb 20. PMID: 38375960.
[666] https://www.oar.nih.gov/nih-hiv-research-program/hiv-aging

Although aging is often associated with decline, some individuals, such as centenarians, experience exceptional longevity. One NIA-funded study seeking to understand the factors that contribute to such longevity identified 230 metabolites connected to extreme longevity and 152 metabolites linked with varying mortality risk.[667] Aging-associated metabolites point to nutrition as a source of intervention for healthy aging. Eating a plant-based diet rich in ergothioneine (abundant in mushrooms and asparagus) and flavones (high levels in celery and parsley) was a marker for longevity. Centenarians also had youthful levels of salsolinol found in dark chocolate and other foods as well as flavones (common in spices and some yellow and orange fruits and vegetables). These results suggest that eating certain foods and following specific dietary patterns may contribute to a long, healthy life. Additionally, metabolic profiles of centenarians highlight the role of *ApoE2*—a well-established longevity gene involved in fat and cholesterol metabolism—in achieving longevity.

NIA, along with NICHD, and NCATS also fund the Long Life Family Study, which is focused on identifying protective genetic or molecular factors that influence healthy aging in major domains of the aging process, including cognitive, cardiovascular, metabolic, and inflammatory.[668] The study has enrolled a unique sample of 4,953 participants in 539 pedigrees that are all enriched for familial exceptional longevity. Recent results from an analysis of data on long-lived families found an association between the *MTUS2* gene and Late Onset Alzheimer's Disease.[669] This gene is associated with a protein involved in the development and function of the nervous system.

Health Across the Lifespan and Rehabilitation

NIH is dedicated to understanding how to promote health and longevity for all Americans across all life stages. From childhood through older age, advances in biomedical science are shedding light on how to maintain health, prevent disease, and support recovery. Alongside prevention and wellness strategies, new approaches in rehabilitation are helping people regain function and improve quality of life, ensuring healthier years at every stage of life. Lead by HHS, the Healthy People initiative—refreshed at the beginning of each decade—provides a strategic framework for a national prevention agenda that communicates a vision for improving health by identifying science-based, measurable objectives with targets to be achieved by the end of the decade.[670] Healthy People 2030 is the initiative's fifth iteration. ODP provides input and guidance on Healthy People activities and coordinates Healthy People activities across NIH. In FY22 to FY24, ODP convened meetings for all NIH participants in Healthy People workgroups and represented NIH at Federal Interagency Workgroups. In addition to Healthy People, NIH created the CARE for Health™ program to establish a primary care clinical research network to conduct clinical research in primary care settings.[671] The program supports a network of research networks that actively engage communities to expand opportunities to the front lines of clinical care in rural primary care settings.[672]

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[667] Sebastiani P, et al. Cell Rep. 2024 Nov 26;43(11):114913. Epub 2024 Nov 5. PMID: 39504246.
[668] https://longlifefamilystudy.com/
[669] Xicota L, et al. Alzheimers Dement. 2024 Apr;20(4):2670-2679. Epub 2024 Feb 21. PMID: 38380866.
[670] https://odphp.health.gov/our-work/national-health-initiatives/healthy-people
[671] https://commonfund.nih.gov/clinical-research-primary-care
[672] https://commonfund.nih.gov/clinical-research-primary-care/news/nih-makes-inaugural-awards-begin-building-its-care

Understanding the multidimensional nature of health and disease is key. Health and disease are not separate, disconnected states but instead occur on a path that can move toward health or toward disease. On this path, many factors, including one's biological makeup; unhealthy behaviors, such as poor diet, sedentary lifestyle, chronic stress, and poor sleep; as well as social aspects of life—the conditions in which people are born, grow, live, work, and age—can lead to chronic diseases of more than one organ system. On the other hand, self-care, lifestyle, and behavioral interventions may help with the return to health. In this context, NCCIH has pioneered the concept of whole person health at the NIH, providing a key conceptual infrastructure linking the missions of all NIH ICO's. Whole person health involves looking at the whole person, not just separate organs or body systems, and considering multiple factors that promote health or disease. It means helping and empowering individuals, families, communities, and populations to improve their health in multiple interconnected biological, behavioral, social, and environmental areas. Instead of treating a specific disease, whole person health focuses on restoring health, promoting resilience, and preventing diseases across the lifespan.

Nutrition is one of the key factors for preserving health across the lifespan. In FY23, the NIH Common Fund Nutrition for Precision Health study—powered by the *All of Us* Research Program, in collaboration with 18 NIH ICs—investigated how nutrition impacts individual health and metabolism.[673] As the most comprehensive precision nutrition study of its kind, the study includes three modules: baseline diet and physiological responses, short-term free-living studies, and controlled feeding studies. By the end of FY24, 2,700 participants had enrolled across 14 clinical sites in six states, contributing valuable data to shape personalized nutrition strategies. These insights are driving the development of tailored dietary approaches to improve health outcomes and advance precision medicine.

The concept of "Food is Medicine" refers to an effort to integrate nutrition and health care through medically tailored meals, produce prescriptions, and teaching kitchens with nutrition programs within communities.[674] In FY23, NIH—in collaboration with other HHS agencies, the USDA, and VA—launched a public request for information to gather insight on food as medicine research opportunities and best practices for implementation. A total of 141 respondents, representing academic institutions, healthcare organization, non-profit community-based organizations, professional associations, food manufacturers, producers and growers, and individual constituents provided comments. The robust response to this request illustrates a growing urgency for greater alignment and collective learning to advance food as medicine research and practice.

NIH has two primary offices dedicated to understanding the various aspects of nutrition and dietary supplements that promote healthy living: Office of Nutrition Research (ONR) and Office of Dietary Supplements (ODS), both in DPCPSI within the NIH OD. By co-funding opportunities with other ICOs, these offices have advanced our knowledge of whole person health in relation to food and supplements. In FY22, ONR's Medical Nutrition Implementation Working Group led the *Malnutrition in Clinical Settings: Research Gaps and Opportunities* workshop.[675] The goal of the workshop was to address research gaps and opportunities related to malnutrition in clinical settings and to catalyze research to develop effective

[673] https://allofus.nih.gov/article/announcement-nih-launches-largest-precision-nutrition-research-effort-its-kind
[674] Jury NJ, et al. Am J Clin Nutr. 2025 Apr;121(4):754-757. Epub 2025 Jan 24. PMID: 39900117.
[675] https://www.labroots.com/ms/virtual-event/malnutrition-clinical-settings-research-gaps-opportunities

nutrition interventions. Between FY22 and FY24, ODS led and co-sponsored five workshops, including one on *Precision Probiotic Therapies—Challenges and Opportunities*[676] and another on *Pathways to Prevention – Nutrition as Prevention for Improved Cancer Health Outcomes*.[677] NCCIH also funds research on nutrition, dietary supplements and natural products through the lens of whole person health; complementing and partnering in the efforts of ONR and ODS.

In 2022, ODS established the NIH Dietary Supplement Research Coordinating Committee to increase collaboration among NIH ICOs involved in dietary supplement research.[678] Dietary supplements can beneficially contribute to the intake of nutrient and other bioactives (e.g., probiotics) that help maintain optimal health and risk reduce of disease. The Committee exchanges programmatic and scientific information, conducts collaborative planning, and the implementation of relevant activities and initiatives to stimulate new research and disseminate information on dietary supplement research efforts. As a part of disseminating information, ODS maintains Dietary Supplement Fact Sheets which serve as a trusted, unbiased source of the latest scientific knowledge on dietary supplements, providing clear, evidence-based information entrusted by researchers, scientists, healthcare professionals, and the public. With millions of views, these fact sheets empower consumers and guide healthcare professionals and policymakers in making informed health and nutrition decisions. During FY22-24, ODS prepared new or updated fact sheets on numerous topics including ashwagandha, carnitine, fluoride, iodine, multivitamin/minerals, omega-3 fatty acids, probiotics, selenium, vitamin A, zinc, supplements for immune function, supplements for infectious diseases, and many others.[679] This effort is complemented by NCCIH, which maintains additional fact sheets on natural products and dietary supplements.[680]

To understand how dietary supplements benefit people at the population level, ODS partnered with USDA, FDA, CDC and other NIH ICOs to coordinate the Population Studies Program, which focuses on understanding dietary supplement use at the population level—who uses supplements, why they use them, and how that use affects health.[681] From FY22 to 24, the program funded components in both the National Health and Nutrition Examination Survey[682] and the Medicare Current Beneficiary Survey[683] to improve dietary supplement and nutrition-related data collection. In that same period, the program co-authored 55 scientific papers on dietary supplements and nutrition-related topics.[684] It also funded the National Academies of Sciences, Engineering, and Medicine (National Academies) to develop a 2022

[676] https://www.nccih.nih.gov/news/events/precision-probiotic-therapies-challenges-and-opportunities
[677] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/nutrition-prevention-improved-cancer-health-outcomes
[678] https://ods.od.nih.gov/About/NIHDSRCC.aspx
[679] https://ods.od.nih.gov/factsheets/list-all/
[680] https://www.nccih.nih.gov/health/atoz
[681] https://ods.od.nih.gov/Research/populationstudies.aspx
[682] https://www.cdc.gov/nchs/nhanes/index.html
[683] https://www.cms.gov/data-research/research/medicare-current-beneficiary-survey
[684] https://ods.od.nih.gov/Research/populationstudies.aspx#publications

webinar series titled *Assessing Intake of Food and Dietary Supplements in Older Adults: A Workshop Series*.[685]

In addition to understanding how to promote and maintain health, many efforts at NIH have been dedicated to understanding how to prevent disease and conditions. ODP coordinates the development of NIH-wide efforts to stimulate rigorous prevention research and advance interventions that promote disease prevention and wellbeing. From FY22 to 24, ODP led the development and publication of funding opportunities on Multi-level Physical Activity Interventions to Improve Health and Well-Being,[686] Increasing Uptake of Evidence-Based Screening in Populations Across the Lifespan,[687] and Addressing Evidence Gaps in Screening.[688] ODP also hosted the workshop series, Pathways to Prevention, to identify research gaps in a scientific area of broad public health importance through the use of an unbiased, evidence-based process. From FY22 to 24 topics covered by Pathways to Prevention workshops included: improving rural health through telehealth-guided provider-to-provider communication, nutrition as prevention for improved cancer health outcomes, and identifying risks and interventions to optimize postpartum health.[689]

NIH supported a National Academies Consensus Study that created a *Blueprint for a National Prevention Infrastructure for Mental, Emotional, and Behavioral Disorders*. The blueprint is for a sustainable infrastructure to implement preventive interventions that promote behavioral health.[690] It will also identify funding needs and strategies to support the infrastructure; identify gaps in policy and health services research that may serve as barriers to widespread program implementation; and recommend state and federal policies to support financing and infrastructure (including workforce development and data interoperability) for promoting behavioral health. In a related effort, ODP coordinated the NIH-wide Prevention Scientific Interest groups, a collection of topic-focused sub-groups that work to identify and develop collaborative activities for advancing prevention research at NIH. Four groups were active during FY22 to 24 and focused on a range of NIH-wide relevant topics, including physical activity, tobacco and nicotine research, early disease and risk factor screening, and interventions to prevent or delay onset of comorbid diseases.

ODP also coordinates the NIH Prevention Research Coordinating Committee, an NIH-wide committee that serves as a venue for exchanging programmatic and scientific information of interest to NIH, planning and implementing collaborative activities across NIH, and disseminating information about federal and non-federal activities.[691] The Committee provides a broad perspective on the current state-of-the-science and informs the ODP Director regarding scientific, programmatic, and policy issues. From FY22 to 24, meeting

[685] https://www.nationalacademies.org/our-work/assessing-intake-of-food-and-dietary-supplements-in-older-adults-a-workshop-series
[686] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-24-058.html
[687] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-178.html
[688] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-179.html
[689] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention
[690] https://www.nationalacademies.org/our-work/blueprint-for-a-national-prevention-infrastructure-for-behavioral-health-disorders
[691] https://prevention.nih.gov/about-odp/partnerships-collaborations/prevention-research-coordinating-committee

presentations and discussions on prevention topics and themes included: opioids and the NIH HEAL Initiative, tobacco use, research methods in prevention, federal nutrition research activities, child health, and ongoing updates of NIH and federal partner activities in prevention research.

Utilizing community resources and ideas towards prevention efforts may increase effectiveness of interventions and treatments. The Community Preventive Services Task Force is an independent, non-federal panel of public health and prevention experts that, with technical and administrative support from the CDC, reviews and assesses scientific evidence to develop recommendations on which community-based health promotion and disease prevention approaches work to improve health. Recommendations inform decision-making about policy, practice, and research priorities for community preventive services. ODP serves as NIH's official liaison to the task force by providing input on review prioritization and recommendations, as well as conveying the views, concerns, and needs of NIH. ODP staff also serve on or recommend NIH scientists to serve on systematic review teams and help disseminate and translate recommendations into actions. Over the course of FY22 to 24, ODP provided co-funding support and subject matter expertise to identify task force priority topics and conducted systematic evidence reviews.[692]

Relatedly, the U.S. Preventive Services Task Force (USPSTF), convened and supported by AHRQ, is an independent panel of experts that reviews, assesses, and evaluates scientific evidence on a broad range of clinical preventive health care services—such as screening, counseling, and preventive medications—and develops recommendations for primary care clinicians and health systems that are published in the form of Recommendation Statements.[693] ODP provides scientific input to the USPSTF. During FY22 and 24, ODP worked closely with the USPSTF to implement recommendations from the National Academie's report, *Closing Evidence Gaps in Clinical Prevention*,[694] which ODP and AHRQ also commissioned. In addition to Recommendation Statements, the USPSTF publishes Insufficient Evidence Statements when it is not possible to make a recommendation about the benefits or harms of a service because the scientific evidence is lacking, of poor quality, or conflicting. These statements represent research gaps that need expanded effort and investment, and which NIH is well suited to help resolve. Each year, ODP conducts the Insufficient Evidence Statement Reporting Survey to collect information about current NIH activities that address research needs and gaps in insufficient evidence statements. ODP continues to further develop, refine, and enhance this process.[695] Information from the survey highlights NIH research that is relevant to insufficient evidence statements, providing an opportunity for ICOs to consider how their current and planned research can address evidence gaps, or whether additional activities may be warranted to better inform the evidence-base for USPSTF recommendations.

One aspect of prevention is observing the risks and exposures that can heighten the chances for developing diseases or conditions. In FY22, NIEHS hosted a workshop titled, *Accelerating Precision Environmental Health: Demonstrating the Value of the Exposome* to catalyze the study of the totality of a

[692] https://www.thecommunityguide.org/
[693] https://www.uspreventiveservicestaskforce.org/uspstf/
[694] https://nap.nationalacademies.org/catalog/26351/closing-evidence-gaps-in-clinical-prevention
[695] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/i-statements/nih-research-activities-related-i-statements

person's exposures over the course of their lifespan. Experts from multiple disciplines explored how to advance the science by discussing tools and technologies, biological responses and impact on health, clinical trials, and more. Where an individual lives can also affect risk factors for disease. FIC funded the Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award program to support research capacity development in chronic diseases and disorders across the lifespan in low- and middle-income countries.[696] The program support institutional research training to sustainably strengthen research capacity and to train experts to develop and conduct research on chronic diseases across the lifespan. The goal is to develop and implement evidence-based interventions relevant to their countries and to learn lessons that can be applied to other similar regions, such as U.S. rural populations or those with limited access to health care facilities.

For people living with disability, maintaining and improving health outcomes can be even more challenging. NIH has many efforts to understanding how research, treatments, and rehabilitation can be utilized to give those living with disabilities opportunities for full, healthy lives. The INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome (INCLUDE) Project investigates conditions that affect individuals with Down syndrome and the general population, such as Alzheimer's disease, related dementias, autism, cataracts, celiac disease, congenital heart disease and diabetes.[697] In FY23, the INCLUDE Project made an initial $20 million investment to launch the nation-wide Down syndrome Cohort Development Program. Down syndrome is caused by the presence of an extra copy of chromosome 21, leading to developmental delays and distinct physical features. The program will collect and track health data from more than 2,000 people with Down syndrome across the lifespan. Individuals will be recruited from dozens of research sites across the U.S., to participate in a common study protocol that will collect biological samples, medical information, and other critical health data. This program will advance our scientific understanding of the condition and yield improvements in the health and well-being of people with Down syndrome and the general population as well.[698]

Another set of chromosomal disorders are those related to mutations of the Fragile X Messenger Ribonucleoprotein 1 (*FMR1*) gene, located on the X chromosome. The FMR1 protein is essential for normal cognitive development; mutations can lead to fragile X syndrome, intellectual disability, premature ovarian failure, autism, Parkinson's disease, developmental delays and other cognitive deficits. Despite many remarkable advances in fundamental knowledge about *FMR1*-associated conditions, there remains a need to: identify, characterize, and/or model factors that predict subgroup- or individual-level differences in clinical features and/or responses to specific interventions among affected individuals; identify novel mechanisms and targets for intervention that modulate symptom severity or therapeutic efficacy; and identify and validate translatable biomarkers and/or outcome measures for potential use in clinical trials. The Centers for Collaborative Research in Fragile X and *FMR1*-Associated Conditions aim to broaden understanding of these research priority areas. In FY24, NICHD's funding opportunity for these Centers

[696] https://www.fic.nih.gov/Programs/Pages/chronic-lifespan.aspx
[697] https://www.nih.gov/include-project
[698] https://www.nichd.nih.gov/newsroom/news/102324-INCLUDE-cohort

called for multidisciplinary teams of basic, translational, clinical, and/or data science investigators collaborating to address these complex, difficult-to-solve problems.[699,700]

For people experiencing disability that affects mobility, biotechnology that can support movement and allow for independence is vital. Researchers from the NIH Clinical Center Rehabilitation Medicine Department developed a wearable robotic exoskeleton to provide gait training to children with crouch gait from cerebral palsy, spina bifida, muscular dystrophy, or incomplete spinal cord injury. The exoskeleton was designed to be used for training outside the clinical setting. Launched in FY23, researchers began running a randomized, crossover interventional clinical trial to evaluate the effectiveness of a 12-week gait training program delivered to children at home and in the community using this exoskeleton.[701] The trial is believed to be the first controlled trial in children that delivers robotic gait therapy in an unsupervised community setting.

Some disabilities are acquired later in life through injury or disease. More than 5.6 million people in the U.S. live with limb loss or limb difference. But until recently, clinicians, researchers, hospitals, and others providing support to this community did not have a comprehensive resource of clinical data to help guide decision making and care. NICHD funded the Limb Loss and Preservation Registry, launched in 2022, as the first national database to standardize, collect, measure, and report on outcomes for those with limb loss or undergoing preservation surgery and post-surgical care and rehabilitation.[702] The registry was established to collect and analyze patient data from diagnosis onward by aggregating de-identified data from electronic health records to track individuals through the course of their care. NICHD has also funded work testing a new surgical procedure for below-knee limb amputation that allows for neural control that improves maneuverability of a robotic limb.[703] Compared to a control group who had traditional surgery, patients undergoing the procedure walked faster with their prostheses and were better at climbing stairs and avoiding obstacles. The user can perceive and control the device, almost as if it were part of their residual limb.

Traumatic brain injury (TBI) remains a major public health challenge in the U.S. A large NINDS-funded study found that blood biomarkers measured on the day of TBI can accurately predict a patient's risk of death or severe disability.[704] Researchers collected samples from nearly 1,700 TBI patients from 18 major trauma centers, focusing on levels of GFAP and UCH-L1, which are proteins released from glial cells and neurons after brain injury. The researchers found that the predictive value of the biomarkers was strongest for patients with moderate to severe TBI and that high levels of the biomarkers were strong predictors of poor outcomes, especially among patients with moderate to severe TBI. If confirmed in future studies, these biomarkers could be used to inform treatment or rehabilitation plans for TBI patients.

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[699] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-25-002.html
[700] https://www.nichd.nih.gov/sites/default/files/2019-11/NIH_ResearchPlan_FMR1_2019.pdf
[701] Devine TM, et al. PLoS One. 2024 Jul 8;19(7):e0304087. PMID: 38976710.
[702] https://www.nichd.nih.gov/newsroom/news/091224-limb-loss-preservation-registry
[703] Song H, et al. Nat Med. 2024 Jul;30(7):2010-2019. Epub 2024 Jul 1. PMID: 38951635.
[704] Korley FK, et al. Lancet Neurol. 2022 Sep;21(9):803-813. PMID: 35963263.

In FY23, NIAID-supported researchers identified an attribute of the immune system called immune resilience that helps explain why some people live longer and healthier lives than others.[705,706] Immune resilience involves the ability of the immune system to rapidly launch attacks defending against infectious invaders and respond appropriately to other types of inflammatory stressors, including aging or other health conditions, and then quickly recover, while keeping potentially damaging inflammation under wraps. The researchers discovered that people with the highest levels lived longer than others and were more likely to survive COVID-19 and sepsis, as well as to have a lower risk of acquiring HIV and developing AIDS, symptomatic influenza, and recurrent skin cancer. Women were more likely to have optimal immune resilience compared to men, which is interesting when one considers that the vast majority of people with autoimmune diseases are women. The findings suggest that there is a lot more to learn about why people differ in their ability to preserve optimal immune resilience. With further research, it may be possible to develop treatments or other methods to encourage or restore immune resilience as a way of improving general health.

Cancer

Cancer is a complex group of diseases defined by the uncontrolled growth and spread of abnormal cells. This unchecked growth can result in benign tumors, which do not invade other tissues, or malignant tumors, which can spread throughout the body and cause severe illness or death. These diseases are classified by their cell or tissue of origin and, increasingly, by genetic and molecular characteristics that can guide diagnosis and treatment.

Cancer remains the second-leading cause of death in the U.S., and the burden is substantial: the Surveillance, Epidemiology, and End Results Program projects 2,041,910 new cases and 618,120 deaths across all cancers in 2025.[707] Those numbers translate to around 5,600 diagnoses and 1,700 deaths every day, underscoring the Nation's ongoing public-health challenge. Yet progress is steady; the latest *Annual Report to the Nation* shows overall cancer mortality declined each year from 2001 through 2022.[708] Improvements in prevention, early detection, and treatment—especially in immuno-oncology and targeted therapy—are the major drivers, although differences by race, ethnicity, and geography show that gains are not yet universal.

Regulatory momentum mirrors these scientific advances. In 2024, FDA's Oncology Center of Excellence cleared 49 oncology products, including 18 new medical entities or new biological license applications and 31 new indications for previously approved agents, expanding options across common and rare malignancies.[709] Among the year's highlights was the approval of a new type of "smart drug" for cancer. This is the first treatment of its kind that targets a specific protein (HER2) on cancer cells, no matter where the tumor is in the body, a milestone in precision oncology.[710] These actions reflect streamlined review

[705] Ahuja SK, et al. Nat Commun. 2023 Jun 13;14(1):3286. PMID: 37311745.
[706] Lee GC, et al. J Allergy Clin Immunol. 2021 Nov;148(5):1176-1191. Epub 2021 Sep 8. PMID: 34508765.
[707] https://seer.cancer.gov/statfacts/html/all.html
[708] https://www.cancer.gov/research/progress/annual-report-nation
[709] https://www.fda.gov/about-fda/oce-annual-reports/2024-oce-annual-report
[710] https://www.fda.gov/about-fda/2024-oce-annual-report/ongoing-clinical-oncology-projects-2024

pathways such as Real-Time Oncology Review and Project Orbis, which speed innovative therapies to patients without compromising safety.

Summary of NIH Activities

NIH, led by NCI, invested billions to push progress across the research continuum, from molecular mechanisms and environmental exposures to prevention, screening, treatment, survivorship, and the data and workforce infrastructure that stitches them together. Total NIH funding for cancer was $7.6 billion in FY22, $8.0 billion in FY23, and $8.1 billion in FY24.[711]

Highlights from FY22-24 include SI-ready imaging resources that host >570,000 studies for algorithm training, and prediction modeling showing that adding just 10 minutes of daily moderate-to-vigorous physical activity could avert around 100,000 premature deaths each year.[712,713] NIH also addressed quality-of-life and environmental dimensions: NIH Clinical Center teams launched a high-demand online nutrition toolkit for hereditary diffuse gastric cancer survivors who are navigating life after prophylactic gastrectomy (stomach removal), and NIEHS showed that full glyphosate formulations found in herbicides—but not glyphosate itself—drive DNA-damage signatures, reshaping herbicide-risk assessments.[714,715] Collectively, these cross-disciplinary advances illustrate how NIH's sustained, collaborative investment is converting scientific insight into tangible gains in cancer prevention, diagnosis, treatment, and survivorship for people across the U.S.

Recalcitrant Cancer Research

Recalcitrant cancers are those that are particularly difficult to treat and have a 5-year survival rate of less than 50 percent. In response to the mandate under Sec. 417G (d)(1) of the *PHS Act* to provide information on NIH actions taken to implement scientific frameworks developed with respect to recalcitrant cancer, Appendix H includes the following information on pancreatic ductal adenocarcinoma and small cell lung cancer research: information on FY22, FY23, and FY24 grants funded, assessment of progress in these research fields, and updates on activities in these research field.

Understanding Cancer Biology

Advancing the understanding of cancer biology has been pivotal in shaping new therapeutic strategies, with NIH-supported research playing a vital role in uncovering molecular pathways and cellular mechanisms that guide the development of more precise and effective treatments. Recognizing the debilitating impact of cancer-associated muscle wasting (cachexia), NIAMS-supported researchers coordinated mechanistic studies that illuminate targetable pathways in skeletal muscle. One team showed that breast cancer cells release tiny particles (called extracellular vesicles) containing a molecule called miR-122, which travels to muscle and disrupts a protective protein modification. This leads to imbalanced

[711] https://report.nih.gov/funding/categorical-spending#/
[712] https://www.midrc.org/
[713] Saint-Maurice PF, et al. JAMA Intern Med 2022;182(11):1145-53. PMID: 35072698.
[714] https://ccr.cancer.gov/surgical-oncology-program/clinical-team/diet-and-nutrition-after-gastrectomy-your-plan
[715] Smith-Roe SL, et al. Environ Mol Mutagen 2023;64(4):202-233. PMID: 36880770.

calcium signaling and activates enzymes that break down muscle tissue.[716] Complementing this, investigators revealed that mitochondrial stress emerges before observable muscle mass loss, a finding which supports the idea that mitochondrial damage contributes to the development of cachexia.[717] A third line of work identified the role of a gene called *KLF10* in causing muscle loss in pancreatic-cancer models.[718] Collectively, these discoveries highlight potential interventions that may predict whether a given muscle might be sensitive or resistant to cachexia and may lead to treatments that could improve muscle health in cancer patients.

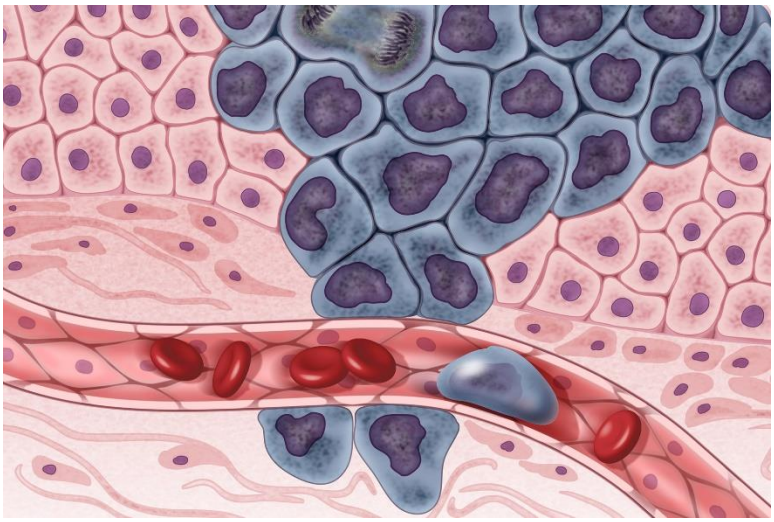


Figure 33. Diagram of growing cancer cells (in purple) surrounded by healthy cells (in pink), illustrating a primary tumor spreading to other parts of the body through the circulatory system. Credit: Darryl Leja, NHGRI/NIH

Leveraging a novel NCATS-engineered approach called Segmentation by Exogenous Perfusion, investigators mapped how the physical position of individual cells within 3D ovarian cancer spheroids can strongly influence which genes are active.[719] Cancer spheroids are 3D cell culture models used to mimic the complex architecture and microenvironment of actual tumors compared to traditional, flat cell cultures. Cells at or near the spheroid surface exhibited heightened proliferation, whereas interior cells showed diminished growth cues, revealing a sharp functional gradient sculpted by the tumor microenvironment. By combining data from fluorescent dyes with detailed genetic analysis of individual cells, the team created a high-resolution atlas that helps explain how a cancer cell's location governs its identity, offering new approaches for therapies that target specific areas within a tumor. These results underscore Segmentation by Exogenous Perfusion's translational potential to decode cancer evolution and refine precision-medicine strategies.[720]

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[716] Yan W, et al. Nat Cell Biol 2022;24(5):793-804. PMID: 35469018.
[717] Delfinis LJ, et al. JCI Insight 2022;7(24):e155147. PMID: 36346680.
[718] Dasgupta A, et al. Proc Natl Acad Sci U S A 2023;120(34):e2215095120. PMID: 37585460.
[719] Morse DB, et al. Cell Syst 2023;14(6):464-481.e7. PMID: 37348462.
[720] https://www.nih.gov/news-events/news-releases/researchers-show-how-tumor-cell-s-location-environment-affect-its-identity

Challenging the dogma that a cell's commitment to divide is a one-way path, NCI researchers showed that human cells can abort cell division and return to a resting state when growth-promoting signals are withdrawn soon after the restriction point, a point that scientists originally thought marked a cells irreversible commitment to division.[721] This plasticity suggests new therapeutic windows to interrupt the growth process by which cancer cells divide quickly and spread. Fundamentally, the work recasts cell-cycle control as a temporal competition instead of an irreversible process, and allows for new research inquiries into how cancer-causing mutations co-opt this flexibility to drive unchecked proliferation.

NCI researchers combined a robotic platform with machine learning to experimentally measure and theoretically model the activation of a population of immune cells called CD8+ T cells. These cells can identify and kill cancer cells, and their activity is regulated by cytokines—proteins that can either stimulate or slow down immune system responses. This process is not fully understood because existing methods do not capture time-dependent dynamics of immune responses.[722] The researchers generalized their approach to multiple immune processes including responses to drug treatments and activation of patient-derived immune cells engineered to attack cancer cells. By training a neural network to specific antigen-induced T-cell activation kinetics, the team developed a quantitative model with which to study high dimensional biological dynamics. Looking ahead, this fusion of robotic sand predictive modeling may one day help to optimize antigen selection for personalized immunotherapies and offers an adaptable blueprint for understanding other high-dimensional cellular responses to cancer.

Ewing sarcoma is an aggressive childhood cancer with limited treatment options, especially for patients whose disease has metastasized (spread to other areas of the body) or recurred after initial therapy. Despite the known dependence of most Ewing sarcoma cases on a specific fusion protein (EWS-FLI), it has proven challenging to inhibit this driver directly. Two NCI-supported research teams have independently identified a promising new target—a protein called ETV6. Using advanced genetic screening techniques, researchers discovered that ETV6 plays a key role in helping Ewing sarcoma tumors grow by influencing the activity of the EWS-FLI fusion protein. Importantly, ETV6 appears to be critical for cancer cell survival, but not for healthy cells, making it an attractive candidate for targeted therapy. These new insights could lead to the development of drugs that block ETV6, offering a new strategy for treating Ewing sarcoma. This discovery may also benefit efforts to treat other cancers driven by fusion proteins.[723,724]

Some of the most common and deadly cancers have mutations in a gene called *KRAS*, including pancreatic, colorectal, and non-small cell lung cancers. A persistent challenge for developing treatments is that *KRAS*-mutant tumors can acquire resistance to targeted inhibitors through the reactivation of extracellular signal-regulated kinase (ERK) proteins that help regulate essential cellular processes like growth and differentiation. To understand how ERK allows these tumors to survive, NCI investigators mapped ERK activity. By cataloguing thousands of molecular signals controlled by the ERK protein in pancreatic cancer cells, the research team established the most comprehensive portrait yet of the mechanisms that drive

[721] Cornwell JA, et al. Nature 2023;619(7969):363-370. PMID: 37407814.
[722] Achar SR, et al. Science 2022;376(6595):880-884. PMID: 35587980.
[723] Lu DY, et al. Nat Cell Biol 2023;25(2):285-97. PMID: 36658220.
[724] Gao Y, et al. Nat Cell Biol 2023;25(2):298-308. PMID: 36658219.

KRAS-mutant pancreatic cancer.[725] This work provides a more complete portrait of how ERK proteins support tumor growth and can be used to help advance therapies that are effective for long-term treatment of *KRAS*-mutant cancers.

Pancreatic ductal adenocarcinoma has a low survival rate and is difficult to treat. Tumors often have a dense, nest-like structure around them that lacks intact blood vessels, creating conditions that decrease the supply of the sugar molecule glucose, an essential fuel source for normal and cancer cells. NCI-supported investigators uncovered that tumors facing nutrient scarcity can rewire their metabolism to use uridine (one of the four molecules that make up RNA) when glucose is limited.[726] In the same study, genetic knock-out of UPP1 (an enzyme involved in uridine metabolism) in model organisms starved tumor cells of energy and slowed their growth, indicating the necessity of uridine to help tumors grow. In support of this, patient data linked high expression of that enzyme to significantly shorter survival, spotlighting UPP1 as a metabolic liability warranting further investigation. By revealing an unexpected fuel source, this work opens the door to potential new therapeutic avenues for one of the deadliest solid tumors.[727]

Solid tumors grow inside a busy "neighborhood" of blood vessels, an extracellular matrix of connective tissue scaffolding, and other different types of cells collectively called the tumor microenvironment. By tracking cell lineages and selectively removing specific cell types in mouse models of pancreatic ductal adenocarcinoma, NCI-supported researchers parsed this neighborhood's connective-tissue residents and uncovered a small subset of cancer-associated fibroblast cells that originate from a type of precursor cell known as pancreatic stellate cells. These stellate-derived cells lay down an especially dense matrix, stiffen the tumor, and block immune-cell entry, thereby giving the cancer cells a decisive growth advantage.[728] The study suggests that signals from nearby cells and molecules, together with differences among cancer-associated fibroblast populations, can lead to functionally distinct subtypes. Additionally, the results provide a basis for future studies to understand the mechanisms of how different cancer-associated fibroblast populations function within tumors and suggest that selectively disabling the most tumor-supportive faction could be an effective therapeutic target.

NCI-supported researchers uncovered that inherited genetic alterations can affect how tumors interact with the immune system in a process called germline-mediated immunoediting.[729] By integrating genetics and computational approaches, this study found that germline-mediated immunoediting shapes breast cancer subtypes and influences how tumors evolve and progress to metastatic disease. These results enhance our understanding of breast cancer origins and uncover biomarkers that could be used to forecast tumor progression and predict a patient's risk of invasive breast cancer recurrence.

Risk Factors

Identifying cancer risk factors is central to advancing prevention and early intervention strategies, with NIH-supported research uncovering genetic, environmental, behavioral, and other contributors to cancer

[725] Klomp JE, et al. Science 2024;384(6700):eadk0850. PMID: 38843329.
[726] Nwosu ZC, et al. Nature 2023;618(7963):151-158. PMID: 37198494.
[727] https://www.cancer.gov/news-events/cancer-currents-blog/2023/pancreatic-cancer-uridine-energy-alternative
[728] Helms EJ, et al. Cancer Discov 2022;12(2):484-501. PMID: 34548310.
[729] Houlahan KE, et al. Science 2024;384(6699):eadh8697. PMID: 38815010.

development. Gastric cancer was once overwhelmingly linked to the bacteria *Helicobacter pylori*, yet incidence has begun unexpectedly rising in younger people in the U.S. and other countries in recent years, even as *H. pylori* prevalence falls. NCI investigators found that the presence of antibodies against specific stomach cells—a hallmark of autoimmune gastritis—more than doubled the risk of intestinal-type gastric cancer in women who were *H. pylori*-negative.[730] The findings suggest a new model in which autoimmune inflammation, rather than infection, may be driving recent trends in gastric cancer incidence rates. This research provides a potential avenue for identifying high-risk individuals for targeted screening and other possible prevention strategies.

Breast cancer survivors face longer-term sequalae when compared to the general public (sequalae are long-term complications or conditions resulting from pre-existing illness or injury that can be linked to side effects from treatment, genetic susceptibility, and/or risk factors). In an NCI-funded metabolomics analysis, researchers found that this may be due to notable differences in serum metabolites, particularly for African American survivors. This study showed that African American breast cancer survivors exhibited changes in three biochemical pathways that are tied to cardiometabolic disease and chronic inflammation, including elevated metabolite levels in two inflammation-related pathways and decreased levels in a lipid metabolism pathway.[731] These results could provide potential clinical targets to reduce long-term sequalae among breast cancer patients.

Meningioma (a tumor that grows from the membranes that surround the brain and spinal cord) is the most common second cancer that develops following radiation therapy to the brain in survivors of childhood cancer. However, the magnitude and modifiers of that risk, along with the impact of chemotherapy, remain uncertain. Supported by NCI, an international analysis showed that in survivors of childhood cancer, the risk of radiation-associated meningioma increased with dose and meningioma risk was higher for children exposed to radiation before the age of 10, with this risk persisting for 30 years.[732] The study also implicated a specific chemotherapy treatment as an additional risk factor. These results strengthen the rationale for today's treatment protocols that limit whole-brain radiation doses and favor techniques that spare healthy tissue in children. Just as importantly, they offer information that could be included in future surveillance guidelines for childhood cancer survivors, especially in those treated at younger ages.

Scientific assays are essential tools in precision medicine, helping researchers understand how toxic exposures—like tobacco smoke—cause genetic mutations that can lead to cancer. The NIEHS/NCI Genome Integrity Consortium is at the forefront of developing faster, more accurate assays to measure how environmental exposures affect DNA and predict individual cancer risk. In a recent study, NIH supported scientists used single-cell whole-genome sequencing to map the accumulation of DNA mutations in lung cells from never-, former-, and current-smokers aged 11 to 86. The study showed that these mutations build up with age and are elevated in smokers, reinforcing how tobacco exposure contributes to lung cancer risk over time.[733] This discovery provides important insights into how lung cancer develops at the

[730] Song M, et al. JAMA Oncol 2022;8(2):268-74. PMID: 34913949.
[731] Luo J, et al. BMC Cancer 2023;23(1):183. PMID: 36823587.
[732] Withrow DR, et al. JAMA Oncol 2022;8(12):1756-64. PMID: 36201196.
[733] Huang Z, et al. Nat Genet 2022;54(4):492-98. PMID: 35410377.

cellular level and may help explain variations in cancer risk among heavy smokers. The study also demonstrates how advanced sequencing technologies can track the effects of environmental exposures on genomic health over time. While single-cell whole-genome sequencing remains primarily a research tool, these findings contribute to our growing understanding of how tobacco exposure drives cancer development and could eventually inform more personalized approaches to cancer risk assessment and prevention strategies.

Glyphosate has been used in the U.S. since 1974 and is one of the Nation's most popular herbicides. Using a battery of complementary *in vitro* assays—including bacterial reverse-mutation, a human TK6 micronucleus test, and a multiplexed DNA-damage panel—NIEHS scientists investigated the potential genotoxic effects of glyphosate and over a dozen related compounds or co-applied herbicides. They found that glyphosate and its primary metabolite, aminomethylphosphonic acid, exhibited no mutagenic or clastogenic activity, in line with prior observations. In contrast, non-glyphosate formulation components, including several co-applied herbicides, showed cytotoxicity and associated DNA-damage signals, indicating that toxicity linked to glyphosate-based formulations stems from components other than the active ingredient. These findings underscore the importance of evaluating complete pesticide formulations and illustrate how high-throughput new-approach methodologies can streamline hazard identification. Collectively, the work provides critical context for ongoing regulatory deliberations around glyphosate safety and supports a formulation-focused approach to herbicide risk assessment.[734]

Screening and Prevention

NIH-supported advances in biomedical research are transforming how cancer is prevented and detected, with particular momentum in the areas of screening and risk reduction. These advances play a role in reshaping cancer prevention strategies, expanding access to screening, and informing policies that can save lives. Published annually, the *NCI Cancer Trends Progress Report* summarizes our nation's advances against cancer in relation to Healthy People targets set forth by HHS. The report, intended for policy makers, researchers, and public health professionals, includes key measures of progress along the cancer control continuum and uses national trend data to illustrate where improvements have been made and where attention is demanded.[735] Along with mortality rates and other standard measures of cancer control, recent reports include updated and new measures that address sleep, melanoma therapies, and systemic therapy treatment for bladder and kidney cancers, illustrating the report's responsiveness to emerging public-health questions. By highlighting opportunities alongside gaps, the report paves the way for future progress against cancer and allows for evaluation of our progress relative to our investment in cancer research discovery, program development, and service delivery.

Through computer modeling, NCI investigators projected the number of deaths that could be prevented if only 10 percent more of the eligible U.S. population used the U.S. Preventative Services Task Force-recommended lung, colorectal, breast, and cervical cancer screening tests.[736] Using Cancer Intervention and Surveillance Modeling Network simulations, they estimated this modest bump could prevent 1,010

[734] Smith-Roe SL, et al. Environ Mol Mutagen 2023;64(4):202-233. PMID: 36880770.
[735] https://progressreport.cancer.gov/
[736] Knudsen AB, et al. JAMA Netw Open 2023;6(11):e2344698. PMID: 37991759.

deaths from lung cancer, 11,070 deaths from colorectal cancer, 1,790 deaths from breast cancer, and 1,710 deaths from cervical cancer—or more than 15,000 lives saved among adults screened in 2021. They also estimated the harms from increased screening, such as false-positive lung scans and mammograms, and colonoscopy complications, allowing decision makers to consider whether the benefits of any screening test outweigh the risks. Overall, these results indicate that the increased uptake of recommended screening strategies would help to reduce the burden of cancer in the U.S.[737]

Launching the Self-collection for Human Papillomavirus Testing to Improve Cervical Cancer Prevention Trial, NCI's Last Mile Initiative is partnering with FDA and pharmaceutical companies to test whether women's self-collected vaginal swabs can safely replace clinician-collected samples and broaden cervical-cancer screening access, particularly in rural and underserved communities.[738] The multi-site trial will rigorously compare accuracy, usability, and cost-effectiveness of patient- versus provider-collected samples.[739] A recent analysis already shows high agreement between self- and clinician-collected specimens, strengthening the scientific evidence for future FDA label expansions and opening new opportunities for improving uptake of cervical cancer screening, especially for people in rural areas.[740]

People with HIV are at much higher risk of developing anal cancer compared to those without HIV. Yet formal screening guidance nationally and internationally was lacking until the NCI-led Anal Cancer/High Grade Squamous Intraepithelial Lesions Outcomes Research trial showed that detecting and treating precancerous growths, known as high-grade squamous intraepithelial lesions, cut the chance of anal cancer developing by more than half.[741] Building on the definitive result from this trial, the International Anal Neoplasia Society convened a multidisciplinary panel that issued the first evidence-based recommendations for routine anal-cancer screening and anal lesions management in adults with HIV.[742] A few months later, a panel of experts in HIV care released new recommendations to prevent anal cancer for people with HIV, including a screening program, partially based on the NCI-led trial results; these were the first U.S. federal guidelines on the topic.[743] Broad adoption and implementation of these guidelines could avert most future cases of anal cancer for high-risk groups.

Launched in 2024, the Cancer Screening Research Network links nine geographically varied academic and community health-care systems to test emerging technologies that can detect cancers before symptoms arise.[744] By embedding trials in settings that serve medically underserved populations—from Veterans Affairs clinics to federally qualified health centers—the network aims to generate screening evidence that truly reflects the U.S. population. Its first effort, the Vanguard Study on Multi-Cancer Detection, will enroll up to 24,000 adults to gauge the feasibility of testing blood-based multi-cancer detection tests in large,

[737] https://www.cancer.gov/news-events/cancer-currents-blog/2024/more-cancer-screening-modeling-study-knudsen
[738] https://prevention.cancer.gov/news-and-events/blog/nci-launches-network-study-self-collection-hpv-testing-prevent-cervical-cancer
[739] Einstein MH, et al. Obstet Gynecol 2023;142(5):1036-43. PMID: 37708516.
[740] Arbyn M, et al. Int J Cancer 2022;151(2):308-12. PMID: 35179777.
[741] Palefsky JM, et al. N Engl J Med 2022;386(24):2273-82. PMID: 35704479.
[742] Stier EA, et al. Int J Cancer 2024;154(10):1694-1702. PMID: 38297406.
[743] https://www.cancer.gov/news-events/press-releases/2022/hiv-hsil-anal-cancer-anchor-study
[744] https://www.cancer.gov/news-events/press-releases/2024/cancer-screening-research-network-launches

randomized controlled trials and to refine logistics such as recruitment, sample handling, and follow-up. Data from this pilot study will inform the design of a subsequent, much larger trial designed to determine whether the use of multi-cancer detection tests reduce cancer mortality and how best to integrate such tests into routine care to achieve this goal.[745]

Detecting cancer early and intervening promptly can change the course of disease progression. When oral cancer is detected early, patients have a five-year survival rate of up to 80 percent, compared to about 20 percent for late-stage disease. The gold standard for oral cancer screening is to biopsy suspicious tissues, which relies heavily on the experience of the clinician. To improve early detection of oral cancers, NIDCR researchers developed a low-cost, portable biopsy guidance system that integrates multimodal optical imaging with deep learning algorithms. It enables real-time projection of cancer risk maps onto oral tissue, guiding clinicians toward high-risk regions for biopsy. By combining widefield autofluorescence imaging and microendoscopy, the system improves biopsy site selection, potentially increasing diagnostic yield and facilitating earlier clinical intervention in resource-limited settings.[746]

Launched in 2023, the Advancing Head and Neck Cancer Early Detection Research program unites NIDCR and NCI to jump-start biomarker discovery and validation studies aimed at detecting oral, pharyngeal, and laryngeal cancers at their earliest, most treatable stages.[747] Seven inaugural projects deploy multi-omics profiling, spatial-omics, and advanced imaging to distinguish benign from premalignant lesions and to flag molecular signatures that herald malignant transformation. Investigators gain streamlined access to the NCI Early Detection Research Network infrastructure, enabling standardized specimen collection, assay harmonization, and robust analytical support that can accelerate translation of candidate markers into clinically deployable tests.[748] By marrying innovative technologies with an NIH-wide resource hub, the initiative lays the groundwork for screening strategies that could raise survival and quality of life for the more than 65,000 Americans diagnosed with head and neck cancers each year.

Several NCI studies showed the benefits of physical activity and healthy behaviors as tools to prevent cancer or premature mortality. One group of NCI epidemiologists used activity monitor data from nationally representative cohorts to estimate that if every U.S. adult added just 10 minutes of moderate-to-vigorous physical activity per day, around 100,000 premature deaths could be prevented annually.[749] A separate analysis revealed that older adults who engage each week in a variety of leisure-time pursuits—from walking and cycling to golf—may have significantly lower all-cause, cardiovascular, and cancer mortality than peers who are not physically active.[750] A third study found that former smokers who pair moderate exercise with other healthy habits (e.g., nutritious diet, moderate alcohol, normal body mass index) reduce their all-cause mortality risks. Evidence-based lifestyle interventions have not been robustly studied in former smokers, and these new findings could have important implications for the 52 million

[745] https://prevention.cancer.gov/major-programs/cancer-screening-research-network-csrn
[746] Coole JB, et al. J Biomed Opt 2023;28(1):016002. PMID: 36654656.
[747] https://www.nidcr.nih.gov/grants-funding/research-funded-by-nidcr-extramural/ahead
[748] https://edrn.nci.nih.gov/about-edrn/mission-and-structure/
[749] Saint-Maurice PF, et al. JAMA Intern Med 2022;182(11):1145-53. PMID: 35072698.
[750] Watts EL, et al. JAMA Netw Open 2022;5(8):e2228510. PMID: 36001316.

former smokers in the U.S.[751] Together, these studies demonstrate that small, attainable increases in physical activities—and broader healthy-lifestyle adherence—can make an impact in reducing the risk of death from cancer and other causes across the U.S. population.

People with breast cancer type 1 susceptibility protein (BRCA1)-associated protein 1 tumor predisposition syndrome (BAP1 TPDS) are at increased risk of developing cancerous tumors of the skin, eye, kidney, and mesothelium (the tissue that lines the chest and abdomen). Recent NIAMS-led research revealed that multiple onychopapillomas—a benign nail tumor—are a clue that the person may also be at risk for BAP1 TPDS.[752] Because BAP1 TPDS confers lifelong risks of uveal (eye) and cutaneous (skin) melanoma, mesothelioma, renal cell carcinoma, and other malignancies, the findings suggest the need for routine nail examinations in individuals with personal or family histories of BAP1-associated cancers, and genetic testing when abnormalities are found.

Long-term NIH cohort data show that prophylactic total gastrectomy (complete removal of the stomach as a preventive measure) dramatically reduced the risk of developing hereditary diffuse gastric cancer, a rare, inherited, and lethal cancer usually caused by mutations in the *CDH1* gene. However, survivors often struggle with marked weight loss, fatigue, and day-to-day functional decline.[753] Endocrine follow-ups reveal accelerated bone demineralization and micronutrient deficits, underscoring the need for lifelong supplements and dietitian-supervised monitoring.[754] To standardize care, an international panel issued consensus schedules for surveillance visits, laboratory testing, and nutrition counseling after the procedure, giving clinicians a shared framework.[755] A commentary from NIH clinicians drawing on interview research with emerging adults weighing surgery highlighted persistent information gaps and argued that registered dietitians play an essential role in helping patients balance cancer prevention with quality-of-life and lifestyle concerns.[756] Building on this work, NIH Clinical Center dietitians and NCI surgeons launched a free online toolkit that walks families through phased meal plans, symptom-management tips, and micronutrient targets.[757]

Surveying U.S. oncologists, an NCI-supported study explored clinician perspectives on the ethical deployment of SI in cancer care. Most oncologists that were surveyed favored educating patients on how SI guides recommendations and supported obtaining explicit consent, reinforcing shared decision-making principles. Many said they would let the patient decide when choosing between physician- and SI-recommended treatment regimens.[758] Together, these insights identify priority areas for future guidelines: rigorous validation, clear patient communication, and clarified lines of accountability as SI tools are increasingly integrated with oncology practice.

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[751] Inoue-Choi M, et al. JAMA Netw Open 2022;5(9):e2232778. PMID: 36136331.
[752] Lebensohn AJ, et al. JAMA Dermatol 2024; Epub 17 May 2024. PMID: 38759225.
[753] Gallanis A, et al. J Clin Oncol 2024;42(4):421-30. PMID: 37903316.
[754] Gamble LA, et al. J Clin Endocrinol Metab 2023;108(10):2635-42. PMID: 36950857.
[755] Roberts G, et al. Gastric Cancer 2022; published online Jul 13. PMID: 35831514.
[756] Gamble LA, et al. J Acad Nutr Diet 2022;122: [epub ahead of print]. PMID: 34968751.
[757] https://ccr.cancer.gov/surgical-oncology-program/clinical-team/diet-and-nutrition-after-gastrectomy-your-plan
[758] Hantel A, et al. JAMA Netw Open 2024;7(3):e244077. PMID: 38546644.

Treatments and Immunotherapies

New discoveries are reshaping cancer care, with advances in targeted treatments and immunotherapies offering more effective and personalized options for some patients. Through the NCI RAS Initiative,[759] two innovative first-in-class compounds targeting *KRAS*-driven cancers have entered clinical trials after receiving investigational new drug approval from the FDA. Both drugs were developed using a structure-guided approach but have different mechanisms of action. The first drug, BBO-10203, began trials in October 2024 and blocks the interaction between multiple forms of *RAS*, a gene commonly mutated in cancer, and another protein involved in cell growth and survival. The second drug, BBO-8520, received Fast Track Designation from the FDA in January 2025 and targets both active and inactive forms of the specific *KRAS* G12C mutation, a common mutation found in several types of cancer. In what could be a significant benefit to patients, BBO-8520 is postulated to delay the development of drug resistance, which commonly occurs with inhibitors targeting only the inactive form of *KRAS* G12C mutants.[760]

Too often, a person's cancer initially responds to standard treatments, but then the cancer returns, necessitating the critical need for alternative treatment options that are tolerable to the patient and effective against the cancer. NCI investigators launched the ViPOR trial, named for the five drugs it includes, to test a combination targeted treatment that does not contain chemotherapy in adults with aggressive B-cell lymphoma, a type of blood cancer, that has become resistant to standard therapies. By hitting multiple molecular pathways that B-cell lymphomas use to survive, the Phase 2 study reported that tumors shrank substantially in 54 percent of patients with 38 percent of those patients' tumors disappearing entirely. This study validates the safety of a concurrent, multitarget treatment approach and shows that it is potentially curative for patients with specific subtypes of B-cell lymphoma.[761,762]

An NCI-supported international clinical trial demonstrated that adding a PARP inhibitor—a class of drugs that target cancer cells by interfering with DNA repair—to standard therapy significantly improved outcomes for patients with BRCA1/2-associated breast cancer. Results from the OlympiA Phase 3 trial showed that one year of the PARP inhibitor olaparib following local treatment and chemotherapy significantly reduced invasive disease recurrence and improved overall survival in patients with a specific type of high-risk early breast cancer with *BRCA1* or *BRCA2* mutations. The treatment was associated with a 38 percent reduction in the risk of death compared to placebo. In March 2022, results from the OlympiA study led to FDA approval of olaparib as an additional treatment following the primary standard therapy for patients with high-risk, BRCA-associated breast cancer.[763]

Cancer immunotherapy is a type of treatment that uses the body's immune system to attack cancer. One way this is done is to genetically modify natural killer (NK) cells—a type of white blood cell with the natural ability to recognize and kill tumor cells—by adding chimeric antigen receptors (CARs), which are receptors engineered by scientists to recognize specific antigens on the surface of cancer cells. In preclinical models,

[759] https://frederick.cancer.gov/initiatives/ras-initiative
[760] https://clinicaltrials.gov/study/NCT06625775
[761] Melani C, et al. N Engl J Med 2024;390(23):2143-2155. PMID: 38899693.
[762] https://clinicaltrials.gov/study/NCT03223610
[763] Tutt ANJ, et al. N Engl J Med 2021;384(25):2394-2405. PMID: 34081848.

NCI-supported scientists discovered that activation of chimeric antigen receptor natural killer cells (CAR-NK) triggers trogocytosis—a cell-to-cell exchange of membrane proteins. This exchange transfers target antigens from tumor cells, onto CAR-NK surfaces, causing CAR-NK cells to attack each other instead of the tumor.[764] This antigen exchange also depletes targets on the tumor surface, which in turn dampens the cancer-killing effect of the treatment and helps explain the muted responses seen in early CAR-NK trials. To counter this problem, the research team co-engineered a second, inhibitory CAR that suppresses self-attack. In preclinical models, these dual-CAR-NK cells successfully inhibited NK cell friendly fire and improved anti-tumor activity suggesting, through this proof-of-concept approach, an extension to the range of therapeutic efficacy for adoptive NK cell therapies.

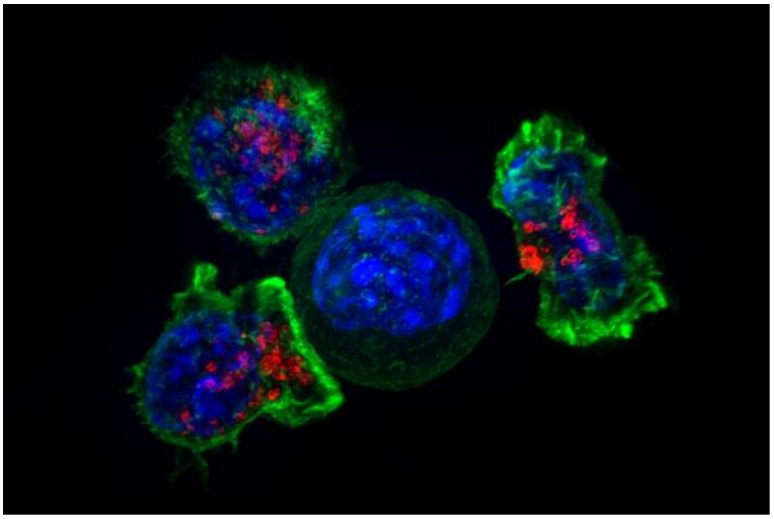


Figure 34. Image of a group of killer T immune cells (green and red) surrounding a cancer cell (blue, center). When killer T cells contact a target cell, they attach and spread over the target and use vesicles (red) to deliver molecules that kill the cancer cell. Credit: Alex Ritter, Jennifer Lippincott Schwartz and Gillian Griffiths, NIH

Tumor-infiltrating lymphocytes are immune cells that migrate into a tumor. A rare subset of these cells, tumor-reactive lymphocytes, can actively identify and kill cancer cells by recognizing mutated proteins, called neoantigens, on the cancer cell surface. In one type of personalized immunotherapy, cells are extracted from a patient's tumor, and tumor-reactive lymphocytes that recognize specific neoantigens are selected for and expanded before being returned to the patient's body to fight the cancer. Identifying the tumor-reactive lymphocytes that recognize neoantigens has been a cumbersome process. However, NCI scientists have developed a new assay that can rapidly predict whether a tumor-infiltrating lymphocyte will be neoantigen reactive based solely on its transcriptomic profile.[765,766,767,768] This approach demonstrates that neoantigen-reactive lymphocytes can be rapidly identified without additional growth,

[764] Li Y, et al. Nat Med 2022;28(10):2133-44. PMID: 36175679.
[765] Lowery FJ, et al. Science 2022;375(6583):877-84. PMID: 35113651.
[766] Hanada KI, et al. Cancer Cell 2022;40(5):479-493.e6. PMID: 35452604.
[767] Zacharakis N, et al. J Clin Oncol 2022;40(16):1741-54. PMID: 35104158.
[768] Leidner R, et al. N Engl J Med 2022;386(22):2112-19. PMID: 35648703.

activation, or testing, thus improving opportunities for bespoke immunotherapies against difficult to treat metastatic solid tumors.

NCI support—through awards made to U.S. small businesses—was instrumental in the 2021 FDA approval of CYTALUX™, the first fluorescence-guided imaging agent that detects ovarian tumors during surgery in real time. FDA approval for lung cancer followed in 2022. CYTALUX binds to folate receptors, which are abundant on tumor cells, and then emits a fluorescent signal caused by a special camera used during surgery. Surgeons administering CYTALUX intra-operatively can now visualize otherwise hard to see cancer deposits. This enables more complete detection of cancer cells for removal and helps to ensure surgical margins are clear, improving the effectiveness of subsequent chemotherapeutic and targeted regimens and overall patient outcomes.[769]

Research at NCI led to a large international clinical trial testing a new treatment option for patients with a previously untreated aggressive type of blood cancer called diffuse large B-cell lymphoma. This cancer occurs when a subset of white blood cells, called B-cells, undergo rapid and uncontrolled growth. The standard treatment is a combination of chemotherapy drugs, a targeted antibody treatment, and a steroid—known together as R-CHOP. The Phase 3 trial tested the benefit of adding ibrutinib, a drug that inhibits the survival and growth of B-cells, to standard R-CHOP therapy. Overall, the trial failed to demonstrate a benefit of ibrutinib in the broader population; however, it did show a 12 percent improvement in survival for younger patients (60 or younger) with a specific type of diffuse large B-cell lymphoma called non-germinal center B-cell. NCI researchers analyzed patient tumor biopsy samples and identified two genetic subtypes that saw especially strong benefits. Based on these findings, the National Comprehensive Cancer Network will consider a recommendation that oncologists add ibrutinib to R-CHOP for younger patients newly diagnosed with non-germinal center B-cell diffuse large B-cell lymphoma, potentially improving their survival outcomes.[770]

Neoantigens are unique proteins found on the surface of cancer cells that arise from mutations in the cancer cell's DNA. They help the immune system identify and mount a response against cancer cells, and because of this are used in cancer vaccines and other immunotherapies. To streamline vaccine development, NCI investigators built pVACtools, which identifies and prioritizes candidate neoantigens.[771] Leveraging the pipeline, the team manufactured multi-epitope DNA vaccines that contain several neoantigens the immune system can target. In a Phase 1 trial for triple-negative breast cancer, the researchers showed the shots were safe, feasible, and elicited neoantigen-specific T-cell responses in 14 of 18 high-risk patients.[772] These advances offer a vaccine development platform for aggressive solid tumors that have few therapeutic options.

Cisplatin is an important chemotherapy cancer drug used in 10 to 20 percent of cancer patients.[773] Although effective, like most broad-spectrum chemotherapy drugs, cisplatin has many side effects,

[769] https://www.cancer.gov/research/leading-progress/stories/cytalux
[770] Wilson WH, et al. Cancer Cell 2021;39(12):1643-1653.e3. PMID: 34739844.
[771] Xia H, et al. Genome Med 2024;16(1):132. PMID: 39538339.
[772] Zhang X, et al. Genome Med 2024;16(1):131. PMID: 39538331.
[773] https://www.cancer.gov/research/progress/discovery/cisplatin

including bone marrow suppression, hearing problems, kidney damage, and vomiting. It causes permanent hearing loss because it remains in the inner ear much longer than other parts of the body.[774] Intramural researchers using an NIDCD-developed model discovered that injecting macrophages, a type of immune cell, into mice reduces cisplatin buildup in both the inner ear and kidneys.[775] The discovered protective effects were linked to decreased platinum accumulation in these tissues (platinum is a key component of the drug). These findings suggest that macrophages play a role in facilitating cisplatin uptake or retention and that targeting macrophages could be a viable strategy to mitigate cisplatin's side effects while preserving its anticancer efficacy.

Research Infrastructure and Collaboration

Biomedical advances in cancer research are dependent on a groundwork of robust infrastructure and powered by strong collaborations. NIH works to support initiatives that bring together varied expertise and resources to drive breakthroughs from the lab to the clinic. Over the last decade, the Barrett's Esophagus Translational Research Network united multidisciplinary teams to curb the rising incidence of esophageal adenocarcinoma by dissecting the biology of its precursor lesion, Barrett's Esophagus, and improving prevention of esophageal cancers. Through expansive genomic, epigenomic, and transcriptomic profiling and the collection of rigorously curated tissue archives, the initiative refined screening criteria, uncovered familial susceptibility genes, and validated diagnostic tools that inform early-intervention strategies. One network study revealed a pathogenic germline mutation that reshapes our understanding of esophageal cancer risk. Another study identified regulators of gene expression in esophageal cancer, revealing potential new biomarkers for early detection and therapeutic targets. Complementing these mechanistic insights, investigators demonstrated in animal models that a specific antioxidant can remodel the esophageal gut microbiome—the community of beneficial microorganisms, such as bacteria, that live in the gut—and reduce reflux-driven tumorigenesis.[776,777] These discoveries are examples of how the network worked to deliver precision detection, tailored surveillance, and innovative treatment strategies against esophageal adenocarcinoma.

A new database developed by NCI scientists links extensive drug activity data from NCATS to detailed molecular information about the cancer cell lines in which those drugs have been tested. The database, called CellMinerCDB: NCATS, expands a set of CellMiner tools that have been freely available since 2009. It is an open web portal that details how 2,675 different compounds affect the growth of cancer cells and includes drug response data from 183 cancer cell lines tested at NCATS. By harmonizing pharmacogenomic data across different repositories, the platform lets investigators explore relationships between cancer cells' molecular makeup and their response to potential therapies in seconds—an invaluable capability for precision treatment design.[778]

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[774] Chattaraj A, et al. JCO Oncol Pract. 2023 May;19(5):278-283. Epub 2023 Mar 15. PMID: 36921239.
[775] Sung CYW, et al. Sci Adv. 2024 Jul 26;10(30):eadk9878. Epub 2024 Jul 24. PMID: 39047106.
[776] Garman KS, et al. Gastroenterology 2023;165(6):1561-1564.e3. PMID: 37659676.
[777] Ravillah D, et al. Gastroenterology 2023;165(2):505-508.e7. PMID: 37182784.
[778] Reinhold WC, et al. Cancer Res 2023;83(12):1941-52. PMID: 37140427.

The NCI Cancer Research Data Commons is a secure, cloud-based data science infrastructure that accelerates cancer research by facilitating data submission, sharing, access, interoperability, and cost-effective analysis at scale. These platforms, called the NCI Cloud Resources, helped lead the effort for global genomic data standards by establishing a unified framework for secure and responsible data sharing in genomics research worldwide, streamlining data ingestion, enhancing user experience, and facilitating file sharing across platforms. As of 2024, the Commons maintained about 10 petabytes of data across 55 million files and provided over 2,000 public tools and workflows to researchers through the NCI Cloud Resources. NCI Cloud Resources also supports training and user adoption, plus established new collaborations with biomedical researchers focused on areas like multi-omics, RNA editing, and cancer biomarker identification.[779]

Comprehensive and meaningful datasets are essential for improving treatments and outcomes for children, adolescents, and young adults with cancer. Through the Childhood Cancer Data Initiative, NCI is transforming how data are collected, analyzed, and shared to accelerate research and discovery. The initiative has launched secure, cloud-based pipelines that integrate pathology images, radiology, genomics, and clinical data, while interactive dashboards make the data accessible to researchers worldwide. A component of the initiative, the Molecular Characterization Initiative was launched in 2022 and has enrolled over 2,000 participants, offering state-of-the-art molecular testing for children, adolescents, and young adults with certain cancer types. Clinical reports and molecular data are submitted directly to the initiative's data ecosystem, where they are paired with detailed information on diagnoses, treatments, and outcomes to support large-scale research. To help researchers prioritize potential therapeutic targets and speed drug discovery, the pediatric Molecular Targets Platform, also released in 2022, offers a searchable knowledgebase linking molecular targets to diseases and drugs.[780] Serving as a central access point, the initiative Hub connects researchers, data scientists, and citizen scientists with tools, datasets, and resources, making it easier than ever to explore and use data to improve childhood cancer care.[781]

The NHGRI-led Clinical Genome Resource plays a vital role in advancing precision medicine by providing expert-curated information on the clinical relevance of genes and genetic variants. Now in its third phase, the resource is expanding its impact by engaging patients, healthcare systems, and genetics professionals; scaling its applications across more clinical specialties; and working to ensure that population databases better reflect all patient populations.[782] In FY24, the Clinical Genome Resource's rigorous evidence assessments were recognized by the American Society of Clinical Oncology, which cited it's expert panels as a key resource in guiding gene selection for hereditary cancer testing panels. This work is supported in part by co-funding from NCI.

To catalyze SI-ready imaging across diseases, NIBIB partnered with the Radiological Society of North America, the American College of Radiology, and the American Association of Physicists in Medicine to

[779] https://datacommons.cancer.gov
[780] https://moleculartargets.ccdi.cancer.gov/
[781] https://datascience.cancer.gov/news-events/news/ccdi-central-hub-links-researchers-childhood-cancer-data-resources
[782] https://www.genome.gov/Funded-Programs-Projects/ClinGen-Clinical-Genome-Resource

establish the Medical Imaging and Data Resource Center.[783] The center aggregates millions of de-identified clinical images with harmonized metadata and makes them accessible through cloud-based SI-training workspaces. Currently, the center is expanding to include more image types, more anatomies, and different disease types with a focus on cancer. So far, more than 570,000 imaging studies have been ingested and over 200,000 have been released to the public to develop SI tools and resources for health care. By setting findability, accessibility, interoperability, and reusability (FAIR) data standards, the center anchors NIH's strategy for scalable, trustworthy imaging SI.

As many as 80 percent of people with cancer experience malnutrition. Malnutrition, a condition caused by not getting the right balance of nutrients such as protein, vitamins, and minerals, can interfere with cancer treatment and increase the risk of complications, hospitalizations, and death. Cancer and cancer treatment can also have nutrition-related side effects like nausea, appetite and taste changes, and fatigue and make it hard for people with cancer to eat well and absorb nutrients from food. To address these challenges, the NIH Office of Nutrition Research (ONR) in DPCPSI within the NIH OD, and its partners convened the NIH Pathways to Prevention Workshop, *Nutrition as Prevention for Improved Cancer Health Outcomes*, and commissioned a systematic review of 206 randomized trials of nutrition interventions delivered before or during cancer treatment.[784] The workshop's output packages the evidence review, panel report, and stakeholder resources, giving clinicians and policymakers a foundation for strengthening the evidence base and over time translating nutrition science into routine cancer practice.

Neuroscience

Neurological diseases are now the world's leading cause of disability and one of the top leading causes of death.[785] An estimated 200 million Americans in 2017, or 6 out of every 10 people, were afflicted by at least one neurological disorder, and as the population ages overall, the incidences of many of these disorders is increasing.[786] 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.

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[783] https://www.midrc.org/

[784] Parsons HM, et al. JNCI Cancer Spectrum 2023;7(3):pkad035. PMID: 37289928.

[785] GBD 2021 Nervous System Disorders Collaborators. Lancet Neurol. 2024 Apr;23(4):344-381. Epub 2024 Mar 14. Erratum in: Lancet Neurol. 2024 May;23(5):e9. Erratum in: Lancet Neurol. 2024 Jul;23(7):e11. PMID: 38493795.

[786] GBD 2017 US Neurological Disorders Collaborators, Feigin VL, et al. JAMA Neurol. 2021 Feb 1;78(2):165-176. PMID: 33136137.

Summary of NIH Activities

Most NIH Institutes and Centers (ICs) and many OD Offices support neuroscience research within their mission and disease focus, and they collectively and collaboratively advance the overall NIH mission. Funding neuroscience research is central to the mission of several NIH ICs, including NIA, NICHD, NIDA, NIDCD, NIMH, and NINDS. NIH spent $11.3 billion on neurosciences in FY22, $11.9 billion in FY23, and $11.8 billion in FY24.[787] Researchers supported by NIH made significant advancements in neuroscience through various innovative projects, many of which were done through the NIH Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative. Collaborations produced resources like detailed brain atlases and connectomes, including the first full wiring map of a fruit fly brain, which advances knowledge of brain function and informs targeted therapy development. These and several other neuroscience advances are discussed in the subsections below, and additional examples can be found throughout Chapter 3.

The NIH BRAIN Initiative®

The NIH BRAIN Initiative, established in 2013, aims to transform neuroscience by advancing and applying cutting-edge technologies to better understand the human brain and inspire new treatments for brain disorders.[788] This cross-cutting, multidisciplinary initiative encompasses 10 NIH ICs, four other federal agencies, and multiple private international organizations, to push the research beyond the capability of any single institute or agency.[789] The BRAIN Initiative recently announced three major transformative projects aimed at revolutionizing neuroscience research and changing the way brain disorders are treated. These new projects include: the BRAIN Initiative Cell Atlas Network, focused on developing a comprehensive atlas of cell types in the mammalian brain; the BRAIN Initiative Connectivity across Scales Network, focused on developing and scaling up the tools necessary to complete a "wiring diagram" of an entire mammalian brain; and the Armamentarium for Precision Brain Cell Access, focused on developing new molecular and gene therapy strategies to study and treat human neural circuit disorders. These initiatives will illuminate foundational principles governing the circuit basis of behavior and inform new approaches to the treatment of human brain disorders.

The coordinated efforts of the BRAIN Initiative, including crucial research conducted between FY22 and FY24, have resulted in the publishing of foundational reference atlases for the fruit fly, mouse, nonhuman primate, and human brains.[790,791,792,793] The result of the first full wiring map—known as a connectome—of an adult fruit fly brain detail over 50 million connections between more than 130,000 neurons, making it the largest connectome of any adult animal.[794] It includes information about different types of brain

[787] https://report.nih.gov/funding/categorical-spending#/
[788] https://braininitiative.nih.gov/
[789] https://braininitiative.nih.gov/about/brain-partners
[790] https://www.ninds.nih.gov/news-events/directors-messages/all-directors-messages/brain-initiative-researchers-complete-groundbreaking-map-fly-brain
[791] https://www.nature.com/collections/fgihbeccbd
[792] https://www.science.org/collections/brain-cell-census
[793] https://www.nimh.nih.gov/news/science-updates/2023/scientists-unveil-detailed-cell-maps-of-the-human-brain-and-the-nonhuman-primate-brain
[794] https://www.nature.com/immersive/d42859-024-00053-4/index.html

cells, their chemical connections (synapses), and how signals travel through the brain. Using advanced electron microscopy, researchers were able to trace how sensory information leads to movement, offering new insights into how a brain controls behavior. For uncovering new knowledge about the human brain, scientists also created the most detailed 3D map of human brain tissue using electron microscopy and SI, reconstructing approximately 150 million neural connections in a tiny brain sample.[795] The Initiative also proactively addresses ethical considerations related to neurotechnology, guided by experts in its Neuroethics Working Group. These valuable resources are freely available to scientists and pave the way for similar connectome projects to better understand the brain and how it works.[796,797]

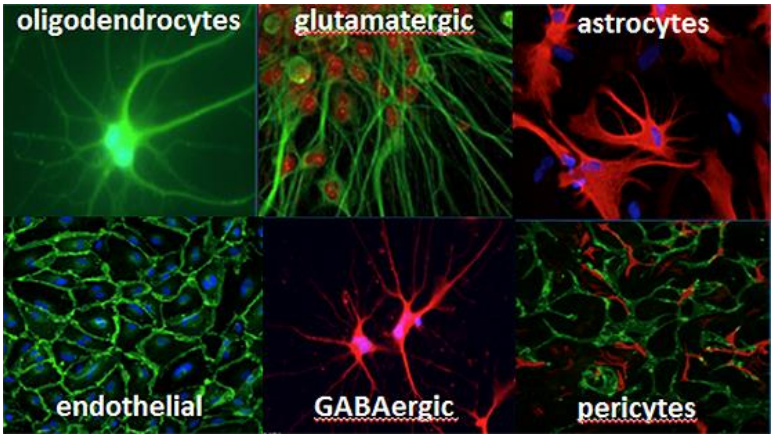


Figure 35. Images of some of the major cell types in the brain. Oligodendrocytes insulate neurons and support nerve signaling, astrocytes support and nourish neurons, endothelial cells form the blood-brain barrier, pericytes maintain blood-brain barrier integrity, GABAergic neurons inhibit activity, and glutamatergic neurons excite activity. Credit: Morgridge Institute for Research in Wisconsin

Findings from these atlases have already enabled advances in understanding the location and function of cell types, comparisons across species, and increases in the scale of technologies used to acquire relevant data. In addition, tools developed through these efforts are having an impact on clinical treatments, as researchers utilize the technologies to gain insights into the cellular basis of Parkinson's disease, Alzheimer's disease (AD), and substance use disorders, which could one day lead to targeted therapies for these and other brain disorders.[798]

To support a more comprehensive mechanistic understanding of the neural basis of behavior, the BRAIN Initiative launched the Brain Behavior Quantification and Synchronization (BBQS) program. BBQS will focus on developing and validating advanced tools and methods to precisely quantify complex behaviors in real-world environments and link them directly to simultaneous neural activity recordings. By enabling a more comprehensive understanding of the causal relationships between brain activity and behavior—particularly for complex, higher-order cognitive functions—BBQS aims to move neuroscience beyond traditional laboratory settings toward the study of naturalistic behaviors and their neural correlates. The

[795] Shapson-Coe A, et al. Science. 2024 May 10;384(6696):eadk4858. Epub 2024 May 10. PMID: 38723085.
[796] Dorkenwald S, et al. Nature. 2024 Oct;634(8032):124-138. Epub 2024 Oct 2. PMID: 39358518.
[797] Schlegel P, et al. Nature. 2024 Oct;634(8032):139-152. Epub 2024 Oct 2. PMID: 39358521.
[798] Gabitto MI, et al. Nat Neurosci. 2024 Dec;27(12):2366-2383. Epub 2024 Oct 14. PMID: 39402379.

insights gained as a result of the BBQS may be particularly relevant for disorders where behavioral interventions can be improved by real-time brain monitoring and feedback. By emphasizing open tools, shared standards, and ethical frameworks, BBQS has the potential to revolutionize neuroscience through more precise, causal, and ecologically valid studies of brain-behavior relationships, ensuring broad utility and responsible use across the field.

Understanding Brain Biology

The brain's complexity presents both profound challenges and opportunities for biomedical research. NIH-supported advances in molecular, cellular, systems, and behavioral neuroscience are deepening our understanding of how the brain works and opening new pathways for diagnosing, treating, and preventing neurological disorders. The brain controls motor skills, thought, emotions, and memory, and understanding its gene activity is key to studying neurological disorders. Researchers from the NIH Common Fund High-Risk, High-Reward Research Program developed a new method to measure gene activity in the brain using engineered reporter proteins.[799] These reporter proteins can move from brain cells into the surrounding fluid and then into the bloodstream, where researchers can more easily measure their levels. The researchers successfully tested this approach in mice, showing its potential for noninvasive study of brain disorders in humans without the need for costly scanners.[800] If validated in humans, this method could enable long-term monitoring of gene activity in the brain.

Alzheimer's disease and related dementias (AD/ADRD) are expected to increasingly impact society as the population ages, making it a significant public health concern. Recent research suggests that AD spreads in the brain due to misfolded tau proteins.[801] NIH-supported researchers used advanced imaging techniques and examined brain tissue to track the progression of the disease over time in nonhuman primates. The researchers found that glial cells in the brain that facilitate neuronal signaling, like microglia and astrocytes, respond to tau at different stages of the disease, with toxicity spreading across neurons by following neural pathways relevant to memory and cognition.[802] The new insights into AD/ADRD progression could inform the development of better treatments.

A recent study supported by the NIH Common Fund High-Risk, High-Reward Program provided insights into the potential role of a protein called RE1-silencing transcription factor in AD. When investigating aged human brain samples, the researchers found that the protein is active in individuals who exhibit early cellular changes associated with AD, and inactive in those who have developed dementia. In mouse models, removal of the protein led to increased brain cell degeneration and memory loss, while the addition of the protein provided protection against cognitive decline typically seen in AD.[803] These findings indicate that RE1-silencing transcription factor plays a role in the earliest stages of AD, acting as a critical checkpoint before the onset of dementia or noticeable cognitive decline. Future research may lay the groundwork for new treatments aimed at protecting cognitive function in patients with AD.

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[799] https://commonfund.nih.gov/newinnovator/highlights/novel-approach-measuring-gene-activity-brain
[800] Lee S, et al. Nat Biotechnol. 2024 Nov;42(11):1717-1725. Epub 2024 Jan 10. PMID: 38200117.
[801] Walker LC, et al. Science. 2024 Sep 20;385(6715):1278-1279. Epub 2024 Sep 19. PMID: 39298592.
[802] Beckman D, et al. Alzheimers Dement. 2024 Aug;20(8):5198-5219. Epub 2024 Jun 21. PMID: 39030748.
[803] Aron L, et al. Nat Commun. 2023 Nov 2;14(1):7030. PMID: 37919281.

Studying centenarians (people who live to at least 100 years old), and superagers (people over 80 years of age with long-term memory performance that resembles a person 20 to 30 years younger), allows researchers to uncover traits and biological mechanisms that might be responsible for healthy aging. NIA launched two initiatives focused on research involving centenarians and superagers: the Resilience/Resistance against Alzheimer's Disease in Centenarians & Offspring Initiative and the Super Aging Research Initiative.[804,805] These initiatives aim to support multi-site studies of older adults with superior cognitive performance to better understand the behavioral, neurological, health, genetic, environmental, and lifestyle factors that promote and sustain cognitive and brain function in advanced age. Results could shed light on new ways to promote healthy brain aging.

In a recent study, researchers supported by NINDS and NIA discovered direct connections between the brain and its tough protective covering, known as the dura mater—the outer layer of which is closely adhered to the inner surface of the skull. These connections, called arachnoid cuff exit points, form where veins cross the barrier separating the brain from the dura. The exit points allow fluids, waste, and immune cells to move between the brain and the dura, enabling waste clearance and immune surveillance. This finding challenges the longstanding belief that the brain is completely sealed off from its surroundings by protective barriers. Using advanced imaging in both humans and mice, research teams found that exit points play a crucial role in regulating brain health by supporting waste drainage and immune interactions.[806] The study also showed that arachnoid cuff exit points become leakier with age, which may increase the risk of neurodegenerative diseases like AD and multiple sclerosis. This new understanding of the brain's drainage and immune pathways could lead to novel strategies for protecting brain health and treating neurological diseases.

Although most children who stutter eventually outgrow the condition, about 25 percent experience persistent developmental stuttering. A recent study supported by NIDCD looked at brain activity in children who stutter and those who do not, focusing on parts of the brain involved in speech.[807] The results showed that children who stutter had reduced activity in the brain's left premotor cortex, an area that helps plan speech movements. They also showed an age-related decrease in activity in the left putamen and thalamus—parts of a circuit that helps regulate and relay motor signals. These findings suggest that functional deficits in the brain's core motor communication loop during speech preparation and production may explain why some children continue to stutter as they get older. Better understanding of the specific neural mechanisms involved in persistent stuttering may lead to precision medicine approaches that improve outcomes.

Scientists supported by NINDS and NIA are learning more about certain hidden pieces of genetic material called cryptic exons.[808] This genetic material surfaces when a protein called TDP-43 does not work properly.[809] NINDS researchers showed that such cryptic exons can lead cells to make abnormal proteins,

[804] https://reporter.nih.gov/project-details/10713947
[805] Rogalski EJ, et al. Alzheimers Dement. 2025 Jan 3;20(Suppl 3):e090906. PMCID: PMC11709875.
[806] Smyth LCD. Nature. 2024 Mar;627(8002):165-173. Epub 2024 Feb 7. PMID: 38326613.
[807] Chow HM, et al. Neuroimage Clin. 2023;38:103413. Epub 2023 Apr 20. PMID: 37099876.
[808] Mehta PR, et al. Mol Neurodegener. 2023 Mar 15;18(1):16. PMID: 36922834.
[809] Seddighi S, et al. Sci Transl Med. 2024 Feb 14;16(734):eadg7162. Epub 2024 Feb 14. PMID: 38277467.

which could play previously unknown roles in diseases like amyotrophic lateral sclerosis, frontotemporal dementia, AD, and Limbic-predominant age-related TDP-43 encephalopathy (LATE). They might also be used as biomarkers to aid early disease detection.[810] Researchers are using these new discoveries about cryptic exons to develop targeted treatments for these conditions.

Risk Factors and Prevention

Understanding the risk factors that contribute to neurological conditions is essential for shaping effective prevention strategies. NIH-supported advances in neuroscience research are revealing genetic, environmental, and behavioral influences that inform prevention strategies. For example, insulin resistance is linked to an increased risk of developing AD/ADRD, but the impact of dietary changes on cognition and overall health remains unclear. NIA- and NIMH-supported researchers compared the effects of the 5:2 intermittent fasting diet (eat normally for five days and restrict calorie intake to 500-600 calories for two days) and the U.S. Department of Agriculture's healthy living diet (emphasizes healthy dietary choices like fruits, vegetables, and lean proteins while limiting added sugars, saturated fats, and sodium) on brain health. They conducted an eight-week clinical trial involving 40 older adults with insulin resistance who were randomly assigned to one of the two dietary plan groups.[811] While both diets were found to reduce the pace of brain aging and improve cognition and insulin resistance, the intermittent fasting diet led to greater weight loss and some additional cognitive benefits. Although AD biomarkers in cerebrospinal fluid did not change with either diet, results still suggest that diet may promote brain health in older individuals.

Problems with how muscles make energy are linked to a higher risk of future memory and thinking problems. NIA-supported scientists examined the relationship between the functioning of muscle mitochondria—known as the powerhouse of cells as they produce the main cellular energy source—and changes in the brain over time. They found that higher skeletal muscle oxidative capacity—the ability of muscles to produce energy—was associated with reduced loss of brain tissue, slower brain aging, and less shrinkage in important brain regions involved in movement, sensation, and memory.[812] These findings suggest that having healthy mitochondria in muscles may protect against neurogenerative diseases.

Not all groups of people have the same likelihood of developing AD/ADRDs. For example, Black individuals are disproportionately affected by higher rates and earlier onset of AD/ADRDs.[813] There are also well-documented differences in sleep across different populations, with Black individuals having higher rates of obstructive sleep apnea and sleep disturbances, including short and long sleep durations and poorer sleep efficiency.[814] Adequate sleep is key to the proper function of the human body and sleep dysfunction and insufficient sleep are associated with AD/ADRD.[815] An NHLBI supported study found that poor sleep

[810] Irwin KE, et al. Nat Med. 2024 Feb;30(2):382-393. Epub 2024 Jan 26. Erratum in: Nat Med. 2024 May;30(5):1504. PMID: 38278991.
[811] Kapogiannis D, et al. Cell Metab. 2024 Aug 6;36(8):1668-1678.e5. Epub 2024 Jun 19. Erratum in: Cell Metab. 2024 Aug 6;36(8):1900-1904. PMID: 38901423.
[812] Tian Q, et al. Nat Commun. 2024 Dec 30;15(1):10786. PMID: 39737971.
[813] Lennon JC, et al. Alzheimers Dement. 2022 Aug;18(8):1461-1471. Epub 2021 Dec 2. PMID: 34854531.
[814] Chen X, et al. Sleep. 2015 Jun 1;38(6):877-88. PMID: 25409106.
[815] Lv YN, et al. Front Neurol. 2022 Dec 14;13:1053942. PMID: 36588906.

quality and waking up frequently during the night were connected to worse thinking and memory skills,[816] and suggests that efforts to improve sleep could help prevent AD/ADRD and reduce health differences between populations who get differing amounts of sleep.

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal disease that destroys nerve cells controlling muscle movement, including those needed for breathing. About 10 percent of ALS cases are inherited, with mutations in the *SOD1* gene accounting for 13 to 20 percent of these cases. In 2023, the FDA approved tofersen (Qalsody), a precision medicine that binds to the messenger RNA produced by the faulty *SOD1* gene and blocks production of the harmful protein.[817] NIH played a crucial role in this breakthrough over the past 30 years by providing leadership and funding for key discoveries, including identifying the *SOD1* gene's role in ALS, developing animal models to study the genes role, validating biomarkers, and supporting therapy development.[818] The first prevention trial for *SOD1*-linked ALS is now underway to study tofersen's long-term effects and NIH continues to support research into new genetic therapies and innovative approaches to treat ALS.

Multiple system atrophy is a rare, adult-onset neurodegenerative disorder with limited treatment options and poorly understood genetics. NIH-supported researchers analyzed whole genome sequences from 888 European-ancestry cases and 7,128 controls to uncover the genetic basis of the disease.[819] The researchers identified four new genetic risk loci and highlighted specific genes linked to increased susceptibility to multiple system atrophy. The study's publicly available dataset will be shared with the scientific community to advance research into the causes and treatment of multiple system atrophy and other brain disorders.

Organophosphorus flame retardants are widely used in household products to reduce fire risk, but there is limited information about their potential effects on brain development, especially in children. To see if these flame retardants could harm the developing brain, NIEHS-supported scientists tested a new developmental neurotoxicity screening battery that uses 22 new approach methodologies to measure acute neurotoxicity critical processes. They found that some compounds can be just as harmful as older, currently banned flame retardants.[820] The researchers also found that levels of these chemicals in people—especially in infants and young children—could reach amounts that cause effects in the lab, raising concerns about their safety. Additional research is needed to fully understand the risk factors of organophosphorus flame retardants on human brain development.

Detection and Diagnosis

Timely and accurate detection of neurological conditions is essential for effective intervention. NIH-supported advances in neuroscience research are driving innovations in imaging, biomarkers, and digital tools that improve diagnostic precision and enable earlier treatment. Diagnosing Parkinson's disease before symptoms appear is challenging because more than 60 percent of dopamine neurons must be lost

[816] Troxel WM, et al. J Alzheimers Dis. 2022;87(4):1591-1601. PMID: 35527545.
[817] Xie Q, et al. Transl Neurodegener. 2025 Apr 16;14(1):19. PMID: 40234983.
[818] https://www.ninds.nih.gov/about-ninds/what-we-do/impact/ninds-contributions-approved-therapies/tofersen-qalsodyr-amyotrophic-lateral-sclerosis
[819] Chia R, et al. Neuron. 2024 Jul 3;112(13):2142-2156.e5. Epub 2024 May 2. PMID: 38701790.
[820] Kreutz A, et al. Toxics. 2024 Jun 18;12(6):437. PMID: 38922117.

before signs of the disease become visible. NIEHS-supported scientists developed a new method to detect early Parkinson's disease that involves stimulating dopamine neurons using two FDA-approved drugs (haloperidol and methylphenidate) and measuring the presence of specific chemicals in mice's spinal fluid and blood.[821] The research team is hopeful that this newly developed method can be adapted to provide a simple and non-invasive test for detecting early-stage Parkinson's disease in humans; but that before that can happen they need to find a safer alternative to using the drug haloperidol, which has known side effects.

Alpha-synuclein is a protein in the brain involved in neuron signaling and that can become abnormal in certain diseases, such as Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, and pure autonomic failure.[822] These diseases, called synucleinopathies, are difficult to diagnose with current methods so there is an urgent need for a reliable, objective biomarker that can be used for diagnosis. Researchers funded by NINDS and NIA tested whether a simple skin biopsy could help detect these diseases by looking for the abnormal form of alpha-synuclein.[823] Results showed that the skin biopsy identified a specific version of alpha-synuclein in 92.7 percent of Parkinson's cases, 98.2 percent of multiple system atrophy cases, 96 percent of dementia with Lewy bodies cases, and 100 percent of pure autonomic failure cases. Importantly, it only identified the alpha-synuclein version in 3.3 percent of people without these diseases, suggesting that skin biopsy is a highly sensitive and specific test for synucleinopathies.[824] Additional research is needed to confirm these results in broader populations and determine how to use the test in clinical practice.

AD has posed a significant health challenge for decades, remaining difficult to diagnose and monitor over time. Traditionally, diagnosis of AD required autopsy and postmortem examination of the brain. NIA-supported researchers evaluated the accuracy of a blood biomarker, plasma phosphorylated tau 217, for detecting AD in living individuals.[825] In a study involving 786 participants across three cohorts, the blood biomarker test demonstrated high accuracy in identifying both abnormal amyloid and tau protein buildup. Its reference ranges were consistent across groups and could reduce the need for invasive confirmatory tests by about 80 percent. Importantly, monitoring over time showed that blood biomarker levels increased only in those with existing amyloid pathology, supporting its usefulness for early and ongoing detection of AD, even before symptoms arise. Also focused on developing diagnostics for AD, support provided through NIA's Small Business Research Program facilitated the transition from basic research to the validation and commercialization of the PrecivityAD™ blood test, which aids in detecting AD in patients.[826] In 2023, the second-generation version was released—the PrecivityAD2™ blood test that measures both amyloid and tau proteins to help physicians more accurately diagnose AD in older adults.[827]

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[821] Zhou J, et al. NPJ Parkinsons Dis. 2021 Dec 16;7(1):116. PMID: 34916526.
[822] Koga S, et al. Mol Neurodegener. 2021 Dec 18;16(1):83. PMID: 34922583.
[823] Gibbons CH, et al. JAMA. 2024 Apr 16;331(15):1298-1306. PMID: 38506839.
[824] https://www.nih.gov/news-events/nih-research-matters/skin-test-detects-evidence-parkinsons-related-disorders
[825] Ashton NJ, et al. JAMA Neurol. 2024 Mar 1;81(3):255-263. PMID: 38252443.
[826] https://www.nia.nih.gov/news/small-business-spotlight-c2n-diagnostics-blood-test-detects-alzheimers
[827] Meyer MR, et al. Alzheimers Dement. 2024 May;20(5):3179-3192. Epub 2024 Mar 16. PMID: 38491912.

The test is currently available to many doctors across the U.S. and is being utilized in clinical trials to evaluate new AD treatments.

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a brain disorder that often manifests with memory loss and dementia symptoms clinically indistinguishable from AD. Recent research supported by NIA has revealed that AD and LATE frequently co-occur in older adults.[828] In this large-scale study, researchers compiled autopsy, genetic, and clinical data from over 6,000 participants to determine how prevalent LATE is across the full spectrum of AD severity. Their analysis showed that nearly 40 percent of participants had LATE at autopsy. The likelihood of LATE appeared to increase with more severe AD, but notably, LATE was also found in about one-quarter of brains with little or no AD pathology. LATE among study participants was strongly associated with cognitive impairment regardless of the severity of coexisting AD. These results could help inform better detection and management strategies for people with LATE, AD or co-occurring LATE and AD.

As mentioned, the brains of people with AD frequently harbor additional pathologies such as Lewy body dementia, cerebral amyloid angiopathy, and LATE. Reliable detection of these non-Alzheimer's pathologies was difficult until researchers from the NIA-supported Alzheimer's Disease Neuroimaging Initiative project developed a multilabel Magnetic Resonance Imaging (MRI)-based classifier that accurately identifies LATE, Lewy body dementia, and cerebral amyloid angiopathy with accuracies between 81 and 93 percent.[829] Investigators also used a technique to detect abnormal alpha-synuclein in the cerebrospinal fluid of participants with Lewy body dementia.[830] Together, these advances open new avenues for disease detection, precision diagnosis, and monitoring treatment response in AD and other co-occurring neurodegenerative diseases.

Diagnosing AD/ADRD continues to be a clinical challenge, particularly because a significant proportion of individuals with dementia remain undiagnosed. The electronic health record (EHR) Risk of Alzheimer's and Dementia Assessment Rule was developed to identify older adults at risk for undiagnosed dementia using routinely collected clinical data.[831] NIA-supported researchers were able to evaluate the accuracy of the rule in two healthcare systems and found it to be a promising decision-support tool for identifying older adults at risk of undiagnosed dementia.[832] Its validated performance across different health systems and populations show the potential for integrating the EHR Risk of Alzheimer's and Dementia Assessment Rule into clinical workflows to support targeted cognitive assessments and reduce differences in dementia diagnosis.

The NINDS DetectCID Consortium is dedicated to advancing the diagnosis and management of dementia within primary care settings.[833] In 2024, the consortium's first large Phase 2 clinical trial found that implementing a five-minute cognitive assessment alongside a structured follow-up care decision tree tripled the likelihood that patients would receive dementia-related care within 90 days, compared to

[828] Nelson PT, et al. Acta Neuropathol. 2022 Jul;144(1):27-44. Epub 2022 Jun 13. PMID: 35697880.
[829] Tosun D, et al. Alzheimers Dement. 2024 Jan;20(1):421-436. Epub 2023 Sep 4. PMID: 37667412.
[830] Tosun D, et al. Alzheimers Dement. 2024 Aug;20(8):5114-5131. Epub 2024 May 21. PMID: 38770829.
[831] Barnes DE, et al. J Am Geriatr Soc. 2020 Jan;68(1):103-111. Epub 2019 Oct 14. PMID: 31612463.
[832] Coley RY, et al. J Gen Intern Med. 2023 Feb;38(2):351-360. Epub 2022 Jul 29. PMID: 35906516.
[833] https://www.detectcid.org/overview

standard care practices.[834] These findings suggest that integrating tools like this into primary care can significantly reduce barriers to diagnosis and improve timely follow-up care for individuals with cognitive impairment. Such changes to medical practice offer the potential to transform dementia care pathways and promote earlier intervention.

With support from NIA, SI-based software for detecting and quantifying Amyloid Related Imaging Abnormalities in AD patients is being developed.[835] In 2024, FDA granted premarket notification clearance for NeuroQuant 5.0 software. The updated software improves visualization and calculations of lesions with new improved deep learning-based technology.[836] This advancement underscores the growing role of SI in medical diagnostics and patient care, paving the way for more personalized and effective healthcare solutions.

Treatments and Therapies

Advancements in treatments and therapies represent a beacon of hope for individuals affected by neurological disorders. Cutting-edge biomedical research innovations, supported by NIH, are transforming the landscape of neurological care, offering new possibilities for effective management and potential cures. Cochlear implants significantly improve communication for individuals with severe to profound hearing loss by stimulating the auditory nerve. However, manual implantation can damage residual hearing in patients. NIDCD-supported scientists have found that robotics-assisted cochlear implant insertion systems result in fewer trauma events and may offer a safer alternative to manual insertions by allowing for lower force, slower insertions, and precise control.[837] Additionally, the use of real-time monitoring during cochlear implant surgery might further enhance the preservation of residual hearing and improve surgical outcomes.[838]

The vestibular system located in the inner ear is crucial for balance, spatial orientation, and the coordination of movement. For about 1.8 million adults worldwide with bilateral vestibular hypofunction, maintaining balance while walking requires constant effort to prevent falls. NIDCD launched a clinical trial that aims to treat this disorder in adults with a vestibular prothesis—a miniature device that includes components worn outside the body as well as implanted into the ear to help restore the sense of balance.[839] The prosthesis works by transmitting signals across the device to electrically bypass malfunctioning areas of the inner ear, partially restoring the sensation of balance.[840] Early results from the trial include improvements in some measures of gait, postural stability, and quality of life.[841]

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[834] Verghese J, et al. Nat Med. 2024 Aug;30(8):2356-2361. Epub 2024 Jun 4. PMID: 38834847.
[835] https://www.prnewswire.com/news-releases/cortechsai-receives-a-new-nih-grant-for-aria-detection-in-alzheimers-disease-302210165.html
[836] https://www.neurologylive.com/view/fda-clears-cortechs-ai-neuroquant-5-software-quantification-segmentation-aria-e-aria-h
[837] Kaufmann CR, et al. Otol Neurotol. 2020 Jun;41(5):631-638. PMID: 32604327.
[838] Claussen AD, et al. Otol Neurotol. 2024 Jun 1;45(5):e459. PMID: 38728567.
[839] https://sites.google.com/site/vestibularneuroengineering/vestibular-implant-trial
[840] Schoo DP, et al. Laryngoscope. 2024 Apr;134(4):1842-1846. Epub 2023 Sep 28. PMID: 37767871.
[841] Chow MR, et al. N Engl J Med. 2021 Feb 11;384(6):521-532. PMID: 33567192.

The vagus nerve is the longest cranial nerve, connecting many organs and regulating basic body functions. Traditional methods for stimulating the vagus nerve involve surgically implanted electrodes. However, through the NIH Common Fund Stimulating Peripheral Activity to Relieve Conditions program, researchers have found a potentially safer, non-invasive method that uses an electrode on the outer ear to increase brain activity in areas responsive to the vagus nerve.[842] This NIH-funded work may lead to a better understanding of specific responses to vagus nerve stimulation in humans and more treatment options for migraine, heart failure, and conditions impacting the muscles in the digestive system.

Prion diseases, such as Creutzfeldt-Jacob disease and mad cow disease, are caused by harmful clumps of misfolded proteins in the brain. Research shows that reducing prion protein levels can halt and reverse disease progression in mice.[843] NIH-funded scientists developed a new tool called Coupled Histone tail for Autoinhibition Release of Methyltransferase to target the prion gene for silencing. It works by recruiting natural enzymes that attach to the prion gene's DNA, effectively turning it off so the harmful protein cannot be made..[844] This new method successfully reduced prion protein levels by up to 80 percent in mice, offering a promising path to developing a strategy for treating prion diseases.

Recent advancements in the quest for effective AD drugs, including two new FDA-approved medications, highlight the direct impact of NIH-funded research. For example, NIA-funded research helped to inform the development of two AD medications approved by the FDA in 2023. Kisunla™ (donanemab-azbt), was shown to be effective in slowing the rates of cognitive and functional decline in participants who have early symptoms of AD.[845] Leqembi (lecanemab-irmb) slowed the rate of cognitive decline by 27 percent in participants experiencing early-stage AD.[846] Continued NIH funding of research will lead to more treatments in the future for AD.

Advanced biomedical imagers, including positron emission tomography (PET) scanners and MRI imagers, have a transformative effect on the study of many diseases by noninvasively imaging biological systems such as the brain, heart, and lungs without the need for biopsies. With capabilities of detecting disease-specific molecules and features, these imagers allow researchers to track and understand both molecular and physiological changes in the progression of many diseases—including lung, prostate and breast cancers, cystic fibrosis, and AD—essential to the development of new treatments. For example, a recent clinical trial tested the efficacy of an antibody drug designed to clear amyloid plaques in patients that showed early symptoms of AD, in which an ORIP-funded advanced PET scanner was instrumental. The PET scanner was used to yield quantitative data about the presence and extent of plaque present in patients that was previously afforded only by autopsy. This allowed researchers the ability to determine the efficacy of the new treatment, and as a result, the antibody drug was granted an expedited approval by FDA.[847] NIH supported advanced biomedical imagers play a vital role in a broad range of biomedical research

[842] Owens MM, et al. J Physiol. 2024 Aug;602(16):4027-4052. Epub 2024 Jul 19. PMID: 39031516.
[843] Minikel EV, et al. Nucleic Acids Res. 2020 Nov 4;48(19):10615-10631. PMID: 32776089.
[844] Neumann EN, et al. Science. 2024 Jun 28;384(6703):ado7082. Epub 2024 Jun 28. PMID: 38935715.
[845] Sims JR, et al. JAMA. 2023 Aug 8;330(6):512-527. PMID: 37459141.
[846] van Dyck CH, et al. N Engl J Med. 2023 Jan 5;388(1):9-21. Epub 2022 Nov 29. PMID: 36449413.
[847] https://orip.nih.gov/about-orip/research-highlights/s10-funded-instrument-yields-data-fda-approval-new-drug-alzheimers

beyond AD that eventually led to better treatments and a healthier living for people with debilitating diseases.

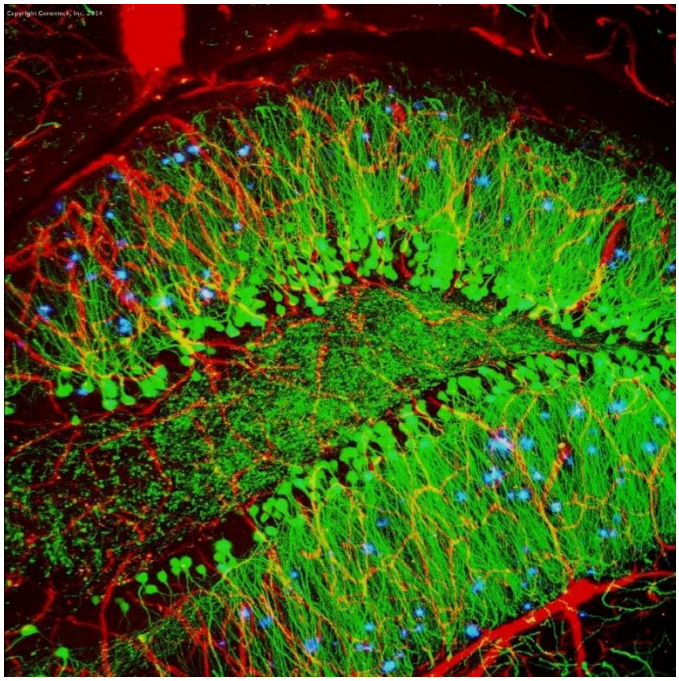


Figure 36. Along with blood vessels (red) and nerve cells (green), this mouse brain shows abnormal protein clumps known as plaques (blue). These plaques multiply in the brains of people with AD and are associated with the memory impairment characteristic of the disease. Credit: Alvin Gogineni, Genentech

In 2022, researchers from an NIH-supported Cryoelectron Microscopy center used advanced imaging technology to study how tau protein clumps, associated with diseases like AD, interact with RNA molecules. The researchers found that RNA binds to tau and helps these harmful clumps stay intact. When RNA was broken down, the researchers observed that tau clumps fell apart, showing that RNA is crucial for their stability.[848] The findings suggest that targeting these RNA molecules could potentially lead to new treatments for neurodegenerative diseases like AD.

Finding new drug targets is important for developing effective treatments for AD/ADRD. In the NIA Drug Repurposing for Effective Alzheimer's Medicines study, researchers looked at Medicare data to see if certain arthritis drugs (tofacitinib, tocilizumab, and TNF inhibitors) affected dementia risk in people with rheumatoid arthritis.[849] Study results showed no statistically significant associations with lowered dementia risk except among participants with heart disease who were treated with TNF inhibitors. While the findings may not be applicable to everyone, they point to the promise of utilizing precision-medicine in specific groups of people at risk for developing AD/ADRD.

[848] Abskharon R, et al. Proc Natl Acad Sci U S A. 2022 Apr 12;119(15):e2119952119. Epub 2022 Apr 4. PMID: 35377792.
[849] Desai RJ, et al. JAMA Netw Open. 2022 Apr 1;5(4):e226567. PMID: 35394510.

Each year, nearly 800,000 people in the U.S. have a stroke, and it is the fourth leading cause of death in the U.S. A stroke occurs when blood flow to the brain is blocked or a blood vessel inside or on the surface of the brain bursts. Researchers from the NIH-supported Stroke Preclinical Assessment Network used rigorous clinical trial methods adapted for preclinical animal research to identify a promising therapy to improve recovery after acute ischemic stroke—which typically happens when a blood clot blocks an artery in the brain.[850] The researchers tested six potential stroke treatments in rodents across six laboratories, employing randomized assignment, predetermined sample sizes, treatment masking, blinded analysis, and assorted animal models. They found that only uric acid met efficacy criteria in behavioral and MRI assessments throughout all phases of the trial, while other candidates were eliminated for lack of effectiveness. The findings suggest uric acid should be further investigated and potentially tested in combination with other therapies, like clot-removal, in humans. The approach demonstrates that collaborative, standardized, and reproducible preclinical trials are feasible, helping to identify therapies with a greater likelihood of success in future clinical trials. The network plans to expand testing of additional stroke therapies in its next research phase.

About half of stroke survivors have persistent disabilities, and stroke is the most common cause of adult disability. Two small studies supported through NINDS and the NIH BRAIN Initiative showed that devices for stimulating the nervous system may provide a new way to help people to recover impaired hand and arm function after stroke.[851,852] In both studies, improvements remained even after turning stimulation off, suggesting the potential for lasting beneficial changes in neural circuits. These findings offer hope that brain and spinal cord stimulation therapies might become effective new options for stroke rehabilitation.

Another disability experienced by stroke survivors is the communication disorder aphasia, which results from damage to the areas of the brain responsible for language. Aphasia affects a person's ability to speak, write, and understand both written and spoken language and can lead to social isolation, reduced participation in rehabilitation, and lower quality of life. NIDCD supports the Center for the Study of Aphasia Recovery to improve outcomes for individuals with aphasia and has made significant progress in understanding recovery mechanisms and the effects of various therapies on aphasia.[853] In its next phase, the Center aims to improve access to and the effectiveness of aphasia therapy, and study health and language factors that influence recovery.

NIH supports many other research avenues aiming to help individuals recover the ability to communicate. For example, researchers funded by NIDCD developed a brain-computer interface to help people with severe speech difficulties. The interface was tested with a 45-year-old man with ALS who could not walk and had severely slurred speech.[854] Four arrays of 64 microelectrodes each were implanted in the participant's brain to record neural activity, which was then decoded in real-time by external computers using an artificial neural network. Initially, the system decoded more than 99 percent of words correctly with a 50-word vocabulary, and after further calibration, it accurately decoded over 90 percent of words

[850] Lyden PD, et al. Sci Transl Med. 2023 Sep 20;15(714):eadg8656. Epub 2023 Sep 20. PMID: 37729432.
[851] Powell MP, et al. Nat Med. 2023 Mar;29(3):689-699. Epub 2023 Feb 20. PMID: 36807682.
[852] Baker KB, et al. Nat Med. 2023 Sep;29(9):2366-2374. Epub 2023 Aug 14. PMID: 37580534.
[853] https://reporter.nih.gov/project-details/10817145
[854] Card NS, et al. N Engl J Med. 2024 Aug 15;391(7):609-618. PMID: 39141853.

with a 125,000-word vocabulary. Over several months, the system's performance improved, maintaining about 97.5 percent accuracy and allowing the participant to converse at a rate of 32 words per minute. This transformative speech brain-computer interface technology provides hope for people who want to speak but cannot and could one day help future patients speak with their family and friends.

Each year, about 18,000 new spinal cord injuries occur in the U.S., with an estimated 255,000 to 390,000 people currently living with a spinal cord injury. NIH-supported researchers identified a rare group of nerve cells called spinocerebellar neurons that attempt to repair themselves and form new connections after injury.[855] By studying these unique neurons, scientists can gain valuable insights into the body's natural mechanisms for nerve repair and regeneration. This discovery paves the way for developing targeted therapies aimed at stimulating or enhancing the self-repair capabilities of these cells, potentially leading to improved recovery outcomes for people with spinal cord injuries. Ultimately, such therapies could help restore function for those affected by spinal cord injury.

The Department of Veterans Affairs (VA) and NIH launched a collaborative study to better understand the chronic, multisystem symptoms of Gulf War Illness, which affects about a third of the nearly 700,000 veterans who served in the Persian Gulf during 1990-91.[856] Some of the neurological symptoms affected veterans experience include fatigue, headache, and memory and cognitive difficulties. This comprehensive research will leverage NIH resources to uncover the biological mechanisms of the disease, with the goal of paving the way for effective treatments. Eligible veterans will undergo extensive testing at the NIH Clinical Center, including protocols designed to trigger and study symptom flares, while VA researchers will maintain a participant data repository and coordinate care. The study focuses on the immune system, autonomic nervous system, and energy-production pathways, and is expected to last five years. By combining expertise and resources, VA and NIH aim to improve care and outcomes for veterans living with Gulf War Illness.

Deep brain stimulation (DBS) is commonly used to treat Parkinson's disease, but traditional approaches lack adaptability to patients' changing neural and clinical states. A small feasibility study funded through NIH's BRAIN Initiative found that adaptive DBS (aDBS)—an implanted device that adjusts stimulation in real time based on brain activity—significantly improved symptom control compared to conventional DBS.[857] Using machine learning and real-time brain signals, aDBS reduced each participant's most bothersome symptoms by about 50 percent. The study only involved four individuals who alternated between conventional DBS and aDBS at home, but most were able to notice improvements during aDBS treatment. Although the therapy currently requires a complex clinical setup, researchers are working to simplify the process and envision a future where automated, self-tuning aDBS could be more widely accessible to patients and clinicians.

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that affects about 30,000 people in the U.S., with most cases being sporadic and leading to death within three to five years of symptom onset. There is currently no cure, but research efforts led by NINDS and supported through initiatives

[855] Matson KJE, et al. Nat Commun. 2022 Sep 26;13(1):5628. PMID: 36163250.
[856] https://www.nih.gov/news-events/news-releases/va-nih-launch-study-gulf-war-illness
[857] Oehrn CR, et al. Nat Med. 2024 Nov;30(11):3345-3356. Epub 2024 Aug 19. PMID: 39160351.

stemming from the *Accelerating Access to Critical Therapies for ALS Act* are advancing new treatment strategies and improving access to experimental therapies.[858,859] These efforts support research and partnerships between the government, scientists, and companies to speed up progress, such as testing new drugs like ibudilast, and setting up programs to share data and resources.[860,861] Recent achievements include FDA approval of the drug tofersen for certain genetic forms of ALS.[862]

Research Infrastructure

In the dynamic field of neuroscience, sustaining and advancing research infrastructure is pivotal to progress, providing the foundation for groundbreaking discoveries and innovations. NIH provides essential support of this vital infrastructure—from state-of-the-art facilities to research resources and cutting-edge tools—to drive forward the frontiers of neurological research. FIC's Global Brain and Nervous System Disorders Research Across the Lifespan Program continues to support collaborative research and capacity-building projects focusing on brain and nervous system disorders affecting low and middle-income countries.[863] Grant recipients develop innovative, collaborative research programs aimed at the long-term goal of building sustainable research capacity. The program helps researchers establish collaborations, build research capacity, conduct pilot studies, and support larger and more complex research studies within institutions, countries, or regions. Knowledge generated through this program—including any new treatments or therapies—will help all patients with neurological disorders, including Americans.

In 2022, the Roy Blunt Center for AD/ADRD opened on the NIH campus in Bethesda, Maryland.[864] Named in honor of Senator Roy Blunt, the Center serves as a hub for global scientific collaboration and innovation in dementia research. The modern 24,000-square-foot facility features advanced laboratories, offices, and conference spaces to foster interdisciplinary teamwork, generate critical resources, and train early career scientists. As a joint initiative of NIA and NINDS, Center programs leverage NIH resources—including the NIH Clinical Center—to complement external research and address key gaps in the field of dementia research. The Center recently established a new stem cell repository to advance research on AD and other neurodegenerative diseases.[865]

In 2024, NINDS announced the launch of two major collaborative neuroscience programs through the Accelerating Medicines Partnership® (AMP®), a public-private partnership between NIH, FDA, multiple biopharmaceutical and life science companies, non-profit and other organizations to transform the current model for developing new diagnostics and treatments. The first new program, AMP in Amyotrophic Lateral Sclerosis (AMP ALS), is building a large open data platform to advance ALS research, develop validated

[858] https://www.congress.gov/bill/117th-congress/house-bill/3537
[859] https://www.ninds.nih.gov/news-events/directors-messages/all-directors-messages/updates-act-als
[860] https://reporter.nih.gov/project-details/11040273
[861] https://fnih.org/our-programs/accelerating-medicines-partnership-amp/amyotrophic-lateral-sclerosis/
[862] https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-amyotrophic-lateral-sclerosis-associated-mutation-sod1-gene
[863] https://www.fic.nih.gov/Programs/Pages/brain-disorders.aspx
[864] https://card.nih.gov/news-events/card-news/roy-blunt-center-alzheimers-disease-and-related-dementias-research
[865] https://card.nih.gov/news-events/card-news/card-and-adni-scientists-are-creating-new-diverse-stem-cell-repository

biomarkers and clinical outcome assessments, and discover new biological targets for ALS therapies and prevention.[866] The second program is an updated version of AMP in Parkinson's Disease and Related Disorders (AMP PDRD), expanding on the existing infrastructure to include a wider range of patients with Parkinson's and related disorders.[867] AMP PDRD seeks to identify biomarkers that distinguish related diseases, aiming to improve diagnosis, accelerate clinical trials, and enable the development of new and personalized therapies.

Astrocytes, the most common cell type in the central nervous system, perform vital functions to maintain nervous system health, such as secretion of neural transmitters and maintenance of the blood-brain barrier. Faulty astrocytes are associated with disorders such as Parkinson's disease, AD, epilepsy, autism, and ALS. Typically, generating astrocytes for research is a delicate and time-consuming process, where radial glial cells first develop into neurons, and then some neurons transform into astrocytes. However, scientists at NCATS and NINDS have successfully used adult stem cells and a novel shortcut to directly create a supply of astrocytes from radial glial cells.[868] This breakthrough could eventually accelerate drug development and regenerative medicine.

The Network for Excellence in Neuroscience Clinical Trials, funded by NINDS, continues to provide infrastructure and support to facilitate efficient development and implementation of multisite Phase 2 clinical trials and biomarker studies for neurological disorders in adult and pediatric populations.[869] The network includes a clinical and a data coordinating center and clinical sites across the U.S., as well as a gene therapy consortium to enable clinical trials on gene-based therapies. In addition to conducting clinical trials, the network supports training and career development for researchers and clinical trial coordinators to strengthen future capacity for clinical trials in neurological disorders.

Translation of candidate therapies for AD disease has been hampered by the poor predictive validity of traditional animal models and insufficient scientific rigor in preclinical research. To address these challenges, the NIA-supported Model Organism Development and Evaluation for Late-onset AD consortium established the Preclinical Testing Core, which implements a systematic and rigorous pipeline for evaluating potential AD therapeutics in animal models. The Core's pipeline incorporates strict quality control measures, comprehensive pharmacokinetic and pharmacodynamic assessments, and unbiased "go/no-go" decision points to enhance the reliability and translational potential of preclinical findings.[870] By addressing longstanding issues in translational research, the Core provides an open resource for the scientific community to nominate compounds for unbiased preclinical testing, with the ultimate goal of improving the success rate of clinical translation in AD disease drug discovery.

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[866] https://www.ninds.nih.gov/current-research/focus-disorders/amyotrophic-lateral-sclerosis/accelerating-medicines-partnershipr-amyotrophic-lateral-sclerosis-ampr-als

[867] https://www.ninds.nih.gov/current-research/focus-disorders/parkinsons-disease-research/amp-parkinsons-disease-and-related-disorders

[868] Jovanovic VM, et al. Stem Cell Reports. 2023 Aug 8;18(8):1701-1720. Epub 2023 Jul 13. PMID: 37451260.

[869] https://www.ninds.nih.gov/current-research/research-funded-ninds/clinical-research/neuronext-network-excellence-neuroscience-clinical-trials

[870] Territo PR.. Alzheimers Dement. 2025 Jan 3;20(Suppl 1):e086531. PMCID: PMC11709537.

Tackling the most ambitious challenges in neuroscience increasingly requires collaboration across varied scientific disciplines and the use of advanced methodologies. To meet this need, NINDS established the Collaborative Opportunities for Multidisciplinary, Bold, and Innovative Neuroscience program in 2024, empowering interdisciplinary teams to address complex neuroscience problems that exceed the capabilities of individual investigators.[871] In its first year, the Program awarded approximately $50 million to six multidisciplinary teams.[872] These awards support research that crosses technical and conceptual boundaries, uniting varied expertise to achieve single, focused, and transformative goals. By fostering collaboration across species, scales, and scientific domains, the program is catalyzing innovation in areas such as lysosomal storage disorders, RNA splicing in neurodegenerative disease, and resilience to cognitive decline.

To improve stroke treatment, prevention, and recovery for people of all ages, NINDS established StrokeNet, a large network of 27 centers and about 500 hospitals across the U.S. to run clinical trials and studies. The network also provides educational opportunities for stroke physicians, clinical trial coordinators, and researchers, fostering a collaborative environment for advancing stroke research and care. In FY24, NIH launched the StrokeNet Thrombectomy Endovascular Platform, which enables the efficient and simultaneous testing of multiple interventions to optimize life-saving treatments for acute ischemic stroke.[873]

In 2024, NIDCD launched the National Smell and Taste Center to advance the understanding of smell and taste disorders through research, patient care, and education.[874] Formed through collaborations among NIH laboratories and clinics, the Center addresses the need for expanded smell and taste research. Center scientists conduct innovative research to understand the mechanisms behind smell and taste and their impacts on health and provide comprehensive care focused on providing compassionate, state-of-the-art interventions for individuals affected by smell and taste disorders. The Center also has a focus on education and outreach to increase awareness and support for individuals affected by sensory disorders.

Research Collaborations

Research collaborations are essential for driving forward groundbreaking research and fostering innovation in the field of neuroscience. NIH supports interdisciplinary partnerships, forums to share ideas, and collaborative networks that are accelerating progress and expanding our understanding of the brain. Tribal consultation emphasizes trust, respect, and shared responsibility, representing an official government-to-government interaction that occurs before any NIH action is taken that can significantly affect AI/AN Tribal Nations and populations. In 2024, the NIH Tribal Health Research Office (THRO) in DPCPSI within the NIH OD facilitated such a consultation prior to the launch of the Alzheimer's Disease and Other Types of Dementia Real-World Data Platform.[875] This consultation allowed Tribal leaders to

[871] https://www.ninds.nih.gov/funding/about-funding/types-research-support/team-or-multi-component/collaborative-opportunities-multidisciplinary-bold-and-innovative-neuroscience-combine-rm1-clinical
[872] https://www.ninds.nih.gov/news-events/news/highlights-announcements/ninds-awards-50-million-team-science-projects-enable-transformative-neuroscience
[873] https://www.nihstrokenet.org/trials/step-trial/home
[874] https://www.nidcd.nih.gov/research/labs/national-smell-taste-center
[875] https://dpcpsi.nih.gov/thro/tribal-consultations/ad-and-dementia-real-world-data-platform

provide critical input on the platform's development. The aim was to ensure that the platform supported Tribal sovereignty and data ownership, and the knowledge and potential dementia treatments derived from the platform were culturally appropriate and applicable to American Indians and Alaska Natives (AI/AN).

In 2022, NINDS and NIA co-hosted the fourth triennial ADRD Research Summit as part of a coordinated effort under the National Plan to Address Alzheimer's Disease.[876] The ADRD summits help establish national research recommendations and set scientific priorities for AD/ADRD. The 2022 Summit specifically addressed research priorities for dementias such as frontotemporal degeneration, Lewy body dementia, multiple etiology dementias, and vascular dementias, while also highlighting cross-cutting topics like ensuring improved health for all.[877] The process included opportunities for public input on draft recommendations, with the final recommendations reviewed, revised, and approved by NINDS Council. Upon approval, these recommendations were adopted as official research milestones within the National Plan, guiding future research and funding priorities.

In 2024, NIA and NINDS co-hosted NIH's Alzheimer's Research Summit, *Building a Precision Medicine Research Enterprise*.[878] The event gathered over 70 top researchers, innovators, and advocates to assess a decade of progress and set goals for the future of precision medicine in AD research. Summit sessions addressed various topics, including disease heterogeneity, risk reduction, participant involvement, translational research, novel therapies, combination treatments, biomarker development, knowledge networks, and regulatory science. Open forums and panel discussions allowed scientists, clinicians, policymakers, and patient representatives to contribute their perspectives. The summit's findings will inform next steps in developing effective, personalized therapies and interventions for AD.

Also in 2024, NIA and the Alzheimer's Association released updated criteria for the diagnosis and characterization of AD.[879] These new guidelines define AD biologically, rather than by symptoms, reflecting advances in biomarker science. According to the new criteria, AD begins as a biological process with neuropathologic changes before any symptoms appear. Clinical symptoms emerge as the neuropathologic burden increases. The new framework provides an integrated approach for determining the extent and severity of AD that combines both biological and clinical information. The updated framework is intended to bridge research and clinical care to improve diagnosis of AD.

While genetic factors are important risk factors for the development of neurological disorders, environmental exposures—many of which are modifiable—play a significant and often underexplored role in the development and progression of these diseases. In 2024, NINDS formed a working group to set research priorities for the neural exposome, or all internal and external exposures that affect brain health over a lifetime.[880] The group recommended six priority actions: identifying relevant exposures, investigating how exposures affect neurological health, studying the impact of exposures in human

[876] https://www.ninds.nih.gov/about-ninds/what-we-do/strategic-plans-evaluations/strategic-plans/alzheimers-disease-related-dementias-summits
[877] https://www.ninds.nih.gov/news-events/events/adrd-summit-2022
[878] https://www.nia.nih.gov/2024-alzheimers-summit
[879] Jack CR Jr, et al. Alzheimers Dement. 2024 Aug;20(8):5143-5169. Epub 2024 Jun 27. PMID: 38934362.
[880] https://www.ninds.nih.gov/sites/default/files/documents/NEXT_WG_Report_FINAL_508.pdf

populations, building a multidisciplinary research community, developing tools and resources, and fostering collaborations. NIH aims to advance this research by engaging the neuroscience community at all stages, from basic science to clinical application, to better understand and address risk factors for neurological diseases.

The *NIH Blueprint for Neuroscience Research* is a collaborative effort across several NIH Institutes, Centers, and OD Offices (ICOs) to support research on the nervous system too challenging for any single IC.[881] Blueprint programs provide funding and resources to academic laboratories and small businesses to support the development of new therapies for nervous system disorders, from early research through initial clinical trials. For example, the BluePrint MedTech program launched in 2022 to support the development of cutting-edge medical devices to diagnose or treat disorders of the nervous system.[882] Several therapies developed through Blueprint programs are now being tested in people for conditions such as fragile X syndrome, a leading cause of inherited intellectual disabilities.

NINDS continues to support the involvement of people affected by neurological diseases in every stage of research, from choosing priorities to sharing results.[883] People with lived experience of conditions like ALS and chronic pain have shaped research plans, served on review committees and working groups, and provided input that has been crucial to projects like the AMP ALS and the NIH HEAL Initiative.[884,885] Involving people diagnosed with neurological diseases or at genetic risk, their loved ones, their caregivers, and those who have lost loved ones to neurological diseases ensures that the research NIH supports is always connected to the people who need it most.

Millions of Americans face significant barriers to accessing care for hearing loss. Untreated hearing loss negatively affects earning potential and overall quality of life, and is associated with increased risk for falls, depression, and loneliness. NIDCD continues to support work that is aimed at improving access to care for hearing loss and addressing issues at the community level.[886] Most recently, NIDCD-supported interventions have been adapted to address the needs of individuals and groups from different backgrounds.[887,888,889]

Microbiome

The human body is home to a vast and complex community of microorganisms—collectively known as the human microbiome—which live on and within us. Far from being harmful, many of these microbes are essential to our health. While bacteria make up the majority, the microbiome also includes fungi, single-

[881] https://www.ninds.nih.gov/current-research/trans-agency-activities/nih-blueprint-neuroscience-research
[882] https://www.ninds.nih.gov/current-research/trans-agency-activities/nih-blueprint-neuroscience-research/bp-medtech
[883] https://www.ninds.nih.gov/current-research/focus-disorders/focus-amyotrophic-lateral-sclerosis
[884] https://www.ninds.nih.gov/current-research/focus-disorders/amyotrophic-lateral-sclerosis/accelerating-medicines-partnershipr-amyotrophic-lateral-sclerosis-ampr-als
[885] https://www.ninds.nih.gov/current-research/trans-agency-activities/ninds-role-heal-initiative
[886] https://www.nidcd.nih.gov/research/improve-hearing-health-care
[887] https://reporter.nih.gov/project-details/10801435
[888] https://reporter.nih.gov/project-details/10831880
[889] https://reporter.nih.gov/project-details/10756576

celled archaea, and even viruses that inhabit places like the nose and gut without causing illness. These microbes, often referred to as commensal organisms, play crucial roles in regulating metabolism, supporting immune function, aiding reproduction, and promoting wound healing. However, when the balance of this microbial ecosystem is disrupted—a state known as dysbiosis—it can contribute to a wide range of health problems, including obesity, diabetes, cancer, and autoimmune disorders. Growing research continues to reveal just how deeply our well-being is intertwined with the tiny life forms that share our bodies.

Summary of NIH Activities

Many NIH ICOs support microbiome research. NIH funding for microbiome research was $917 million in FY22, $957 million in FY23, and $1.0 billion in FY24.[890] 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. This section provides a snapshot of recent advances in microbiome research.

Understanding the Microbiome

Microorganisms play a critical role in health and disease. NIAMS and NIGMS supported scientists found that one potential factor affecting osteoarthritis (OA) is the microbiome.[891] OA is a chronic, age-related musculoskeletal disease that leads to progressive loss of function in joints causing pain, loss of mobility, and early mortality. The researchers previously determined that human and mouse cartilage contain a microbiome and the types of microbes comprising it vary depending on whether the cartilage is affected by OA. In 2023, researchers demonstrated that early OA can influence the type of microbes living in the small intestine. It can also make the wall of the intestine more permeable, which allows the microbes to move into the blood and gather around the joints. It was previously thought that the changes in the intestinal microbiome might cause OA, but this new study shows that OA itself might also cause changes in the intestinal microbiome.

The study of the gut microbiome and its effects on health is a growing field and scientists are learning how the gut microbiome connects to many health conditions, including obesity, metabolic disorders, inflammation, cancer, and depression. Recently, scientists supported by NIAID and NIDDK studied how disruptions in the gut microbial ecosystem might lead to celiac disease in babies at-risk for the disease.[892] Celiac disease is autoimmune disorder primarily affecting the small intestine, where patients develop intolerance to the wheat protein gluten, that causes gastrointestinal problems such as chronic diarrhea, abdominal distention, and malabsorption. In a research project called the Celiac Disease Genomic, Environmental, Microbiome and Metabolomic study, researchers followed these at-risk babies over time. They found that some babies who later developed celiac disease lost certain helpful bacteria in their guts that help to protect against the disease. These results give researchers hope that by changing the types of bacteria in the gut early in life, they might one day be able to prevent celiac disease before it starts. This research might also be applicable to other autoimmune diseases.

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[890] https://report.nih.gov/funding/categorical-spending#/
[891] Izda V, et al. Geroscience. 2024 Apr;46(2):2317-2341. Epub 2023 Nov 9. PMID: 37946009.
[892] Tran T, et al. Pediatr Res. 2024 Apr;95(5):1254-1264. Epub 2024 Jan 4. PMID: 38177249.

There is evidence that the microbiome influences our epigenetics—changes in gene expression that happen without changes to the DNA sequence. Epigenetic changes in gene expression result from the addition or removal of small molecules to specific DNA sequences in response to a biological or environmental stimulus. These small molecules activate or suppress gene expression. To help prepare for future research initiatives in this area, in summer 2023 ONR organized a seminar where scientist convened to explore how dietary intake and metabolism by the gut microbiome can alter one's epigenetics, potentially shaping phenotype and influencing health and disease.[893] The seminar was a collaboration between the Microbiome, Diet, and Health Interrelationships and Foundational Nutrition Science Implementation Working Groups.

Treatments and Therapies

The gut microbiome consists of trillions of bacteria that can help and harm our health. Scientists are learning more about how diet and nutrition shape our gut health. Investigators in the NIH Clinical Center collaborated to develop the Mediterranean-like Unprocessed Diet Intervention Study of the Gut Microbiome of Healthy Adults protocol.[894] The study investigates changes within the gut in healthy adults when switching from a low fiber, high fat diet to a Mediterranean-like diet that includes unprocessed foods. Using the NIH Clinical Center Metabolic Kitchen, investigators created a complex four-week diet where all food items were highly controlled and accurately weighed. The study will provide information on the connections between the gut microbiome and well-being when using a Mediterranean-like unprocessed food diet and may help inform dietary guidelines for healthier eating.

In a related study, scientists supported by NIAID, NIDDK, and the NIH Clinical Center studied how two very different diets—a vegan diet and a ketogenic (low-carb, high-fat) diet—affect the immune system and gut microbes in people.[895] They found that each diet influenced different parts of the immune system: the keto diet boosted immune cells involved in long-term defense, while the vegan diet activated early-response defenses, especially those related to fighting viruses. These changes happened in just two weeks and affected the microbiome and how the body processed nutrients like fats and amino acids that make up proteins. The study showed that diet can rapidly and powerfully shape both the microbiome and the immune system in different ways. These insights could help guide personalized diets as part of future treatments or prevention strategies for disease.

The oral microbiome is also important to understand in the progression and prevention of disease. Certain changes in the bacteria found in the oral microbiome are known to increase the risk of tooth decay. A longitudinal study examined the associations between young children's oral microbiome, tooth decay development, and other risk factors, such as demographics and dietary habits.[896] Researchers supported by NIDCR found that shifts in the oral microbiome associated with tooth decay development can occur as early as three years before the clinical signs of tooth decay. Additionally, researchers found that sampling

[893] https://dpcpsi.nih.gov/sites/default/files/FLYER-ONR-Interactions-Between-Diet-Virtual-Seminar-508.pdf
[894] https://reporter.nih.gov/project-details/11180839
[895] Link VM, et al. Nat Med. 2024 Feb;30(2):560-572. Epub 2024 Jan 30. Erratum in: Nat Med. 2024 Jun;30(6):1785. PMID: 38291301.
[896] Kahharova D, et al. J Dent Res. 2023 Jul;102(7):759-766. Epub 2023 Apr 11. PMID: 37042041.

dental plaque was better at identifying unbalanced oral ecosystems from healthy ones compared to sampling saliva. These findings suggest that early testing of the oral microbiome could help predict and possibly prevent tooth decay in young children.

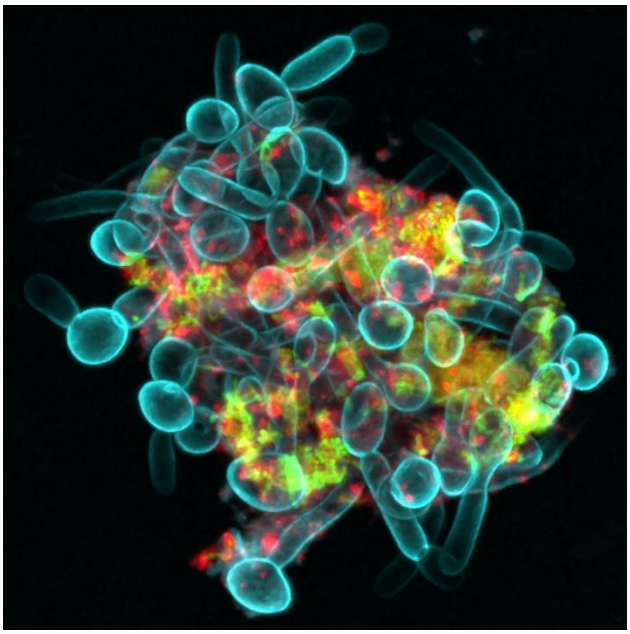


Figure 37. An interkingdom assemblage formed by fungi (Candida albicans in blue), bacteria (Streptococcus mutans in green), and bacteria-derived extracellular polymers (alpha-glucans in red) in human saliva. Credit: Zhi Ren, University of Pennsylvania

Billions of organisms live on the skin and communicate with the host immune system and with each other in a sophisticated network. NIAID researchers discovered that certain harmful bacteria on the skin, like *Staphylococcus aureus*, can trigger a rapid immune response through the toxins they release.[897] These bacterial toxins directly signal immune cells in the blood to rush to the site of infection faster than previously thought. This response does not rely solely on skin cells detecting the bacteria but instead involves direct recognition of toxins by the immune system. A key gene, early growth response protein 1, helps control this fast-acting immune defense. Understanding this toxin-based alert system could lead to new therapies that enhance or mimic this natural defense to prevent or treat skin infections more effectively.

Researchers supported by NIAMS and NIGMS studied patients undergoing spine surgery to understand why surgical site infections still happen despite modern infection prevention efforts. They discovered that most infections came from the patient's own skin bacteria before surgery, rather than from outside sources.[898] Many of these bacteria were resistant to the antibiotics typically used during the procedure. By analyzing the types of microbes and their resistance patterns before surgery, the researchers showed that each patient's unique microbiome plays a major role in infection risk. This suggests that future

[897] Nguyen TH, et al. Nat Microbiol. 2022 Jan;7(1):62-72. Epub 2021 Dec 6. PMID: 34873293.
[898] Long DR, et al. Sci Transl Med. 2024 Apr 10;16(742):eadk8222. Epub 2024 Apr 10. PMID: 38598612.

infection prevention strategies should be personalized based on a patient's own microbiome and antibiotic resistance profile.

Eczema is a chronic inflammatory skin condition that is characterized by dry, itchy skin that can compromise the skin's barrier, which helps to retain moisture and keep out allergens. People with eczema are more vulnerable to bacterial, viral, and fungal infections. Research funded by NIAID led to the development of a topical probiotic treatment for eczema using the naturally occurring skin bacterium *Roseomonas mucosa* to reduce eczema symptoms effectively.[899] Clinical studies showed this treatment to decrease eczema severity by over 75 percent, improve skin barrier function, and reduce reliance on corticosteroids, with sustained benefits observed up to eight months post-treatment. The treatment resulting from this study offers a promising, microbiome-based option for managing eczema in children and adults.

Researchers from NIAMS's intramural research program and NHGRI, in collaboration with international partners, studied the microorganisms that live on healthy human skin. They cataloged a broad analysis of the human skin microbiome into the Skin Microbial Genome Collection.[900] This resource includes about 85 percent of the microbes found on the skin in 19 areas of the body. It helps scientists better understand how skin microbes may help protect against or contribute to disease. The Collection is an important tool for future research on skin health and infections.



Figure 38. Researchers have now identified and catalogued more species of microorganisms that reside on the human skin than has ever been possible, largely due to advances in bioinformatics and laboratory techniques. Credit: Daryl Leja, NHGRI/NIH

NEI supported researchers are interested in understanding how the ocular microbiome affects the health of the front of the eye. The Anterior Segment Initiative's Ocular Surface Innervation Consortium consists of eight teams collaborating to study the ocular microbiome and its contribution to ocular conditions such as corneal pain, tear formation in dry eye, and migraine.[901] Researchers created 3D corneal organoid tissues that mimic proteins and cell types of the developing cornea in the womb. These models can be

[899] https://www.niaid.nih.gov/news-events/niaid-discovery-leads-novel-probiotic-eczema
[900] Saheb Kashaf S, et al. Nat Microbiol. 2022 Jan;7(1):169-179. Epub 2021 Dec 24. PMID: 34952941.
[901] https://www.nei.nih.gov/about/goals-and-accomplishments/nei-research-initiatives/anterior-segment-initiative

used to test safety as new drugs are developed as well as deciphering the role of the ocular microbiome in health and disease.

Autoimmune Diseases

Autoimmune disease occurs when the immune system mistakenly attacks healthy cells, tissues, and organs throughout the body. Approximately 8 percent of the U.S. population (around 25 million people) are living with an autoimmune disease, and nearly 80 percent of those with an autoimmune disease are women. The category of autoimmune diseases includes more than 140 diseases that are chronic and in many cases debilitating—with no known cures.[902] These diseases can affect almost every organ in the body and can occur at any point across the lifespan. Despite their high prevalence and morbidity, many autoimmune diseases are understudied, and treatment options are limited.

Some autoimmune diseases are well known, such as systemic lupus erythematosus (SLE or lupus) and rheumatoid arthritis (RA), while others are rare and difficult to diagnose like Complement, Angiopathic Thrombosis, and Protein-Losing Enteropathy (CHAPLE) disease. More information about NIH research on the autoimmune diseases type 1 diabetes, multiple sclerosis, and inflammatory bowel diseases is available in other sections of this chapter.

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.

NIH supports research on the underlying genetics and immune responses, risk factors, screening, diagnosis, treatment, and management of autoimmune diseases, as well as identifying emerging autoimmune diseases. Because autoimmune diseases span many organ systems and clinical disciplines, the majority of NIH ICs and many OD Offices conduct and support autoimmune disease research. NIH funding for autoimmune diseases research was $1.08 billion in FY22, $1.05 billion in FY23, and $1.02 billion in FY24.[903]

NIH Office of Autoimmune Disease Research

To further accelerate progress in this area, in conjunction with the *FY23 Consolidated Appropriations Act (P.L. 117-328)*, Congress directed NIH to establish an Office of Autoimmune Disease Research (OADR) within ORWH.[904] Since its establishment, OADR-ORWH has spearheaded several initiatives to advance the

[902] National Academies of Sciences, Engineering, and Medicine. 2022. Enhancing NIH Research on Autoimmune Disease. Washington, DC: The National Academies Press. https://doi.org/10.17226/26554.
[903] https://report.nih.gov/funding/categorical-spending#/
[904] https://www.appropriations.senate.gov/imo/media/doc/Division%20H%20-%20LHHS%20Statement%20FY23.pdf

field of autoimmune disease research and fulfill its congressional directives,[905,906] as well as strengthening engagement with advocacy groups, researchers, and members of the autoimmune disease community.[907,908] In FY23 and FY24, OADR-ORWH co-funded 92 awards spanning extramural research, intramural research, intramural scientific fellowships, and workshops. OADR-ORWH strategically supported research across 14 autoimmune disease areas, encompassing 52 different autoimmune diseases. These awards were distributed to 15 different ICs, fulfilling OADR-ORWH's mission to support autoimmune disease research across NIH and enhance resources for new and ongoing research.[909]

In addition, OADR-ORWH established the NIH Coordinating Committee for Autoimmune Disease Research to strengthen coordination of NIH-wide collaborations and optimize autoimmune disease research efforts. For example, OADR-ORWH and partners across NIH, including NIEHS and NLM, are working to increase the number of NIH-endorsed common data elements related to autoimmune disease and to develop a federated data platform for autoimmune disease research. Taken together, these efforts will improve the quality of data collected in NIH-funded autoimmune disease research and enable comprehensive analysis across distributed datasets, speeding the discovery of new knowledge, treatments, and therapies.

Understanding Autoimmune Diseases

Autoimmune diseases are more common in women than in men. Most studies into these sex differences have focused on the role of hormones and gene expression; however, the latest evidence suggests that the immune system may also launch a misguided attack on other molecules that regulate genes. Protein-RNA complexes that include the X-inactive specific transcript—that helps to turn off one of the two X chromosomes in female cells—have emerged as a potential target of the immune system, further highlighting that the factors that contribute to sex differences in autoimmune diseases are complex and varied.[910]

Some autoimmune diseases, including RA and lupus, are heritable, meaning that they can be passed through genes from parents to children. Genome-wide studies are a powerful tool to better understand the genetic component of autoimmune diseases. In FY23, a group of NIAMS researchers and researchers supported by NCATS, NCI, and NHGRI examined a variety of populations from different ancestral groups and geographic locations and found previously unidentified parts of the genome associated with RA and lupus.[911,912] These findings could lead to a better understanding of these disease mechanisms, thus providing the basis for new treatments.

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[905] https://orwh.od.nih.gov/sites/orwh/files/docs/FY23-24%20Report%20of%20the%20Office%20of%20Autoimmune%20Disease%20Research%20in%20the%20Office%20of%20Research%20on%20Women%27s%20Health_REVISED.pdf
[906] https://orwh.od.nih.gov/OADR-ORWH/Strategic-Planning-for-ADR
[907] https://orwh.od.nih.gov/OADR-ORWH/updates-on-oadr-orwh
[908] https://orwh.od.nih.gov/OADR-ORWH/sciencetalks
[909] https://orwh.od.nih.gov/OADR-ORWH/Funding-Information
[910] Dou DR, et al. Cell. 2024 Feb 1;187(3):733-749.e16. PMID: 38306984.
[911] Ishigaki K, et al. Nat Genet. 2022 Nov;54(11):1640-1651. Epub 2022 Nov 4. PMID: 36333501.
[912] Vazzana KM, et al. Genes Immun. 2023 Aug;24(4):200-206. Epub 2023 Jul 24. PMID: 37488248.

While there are many tools available to measure physiologic and organ system function and health, few tools measure immune system health. Physicians can order diagnostic blood testing using an automatic blood counter—developed by NIH-supported researchers in the 1950s and widely used to this day in hospitals and labs around the world[913]—to understand the numbers of specific blood and immune cells, but this is not enough to understand immune function or even diagnose many autoimmune diseases. In FY24, NIAID-supported researchers developed a new tool called the immune health metric, which can measure and, in some cases, predict how the immune system may respond to changes in physiologic health.[914] The researchers hope that in the future this new tool can be used by physicians to predict immune health problems before symptoms appear, thereby preventing autoimmune and other diseases.[915]

Private-public partnerships, like the Accelerating Medicines Partnership, remain a vital tool that enables NIH supported researchers to better understand and advance research into autoimmune diseases. In FY22, the Foundation for NIH and NIH launched the AMP Autoimmune and Immune-Mediated Diseases (AMP AIM) program to deepen our understanding of the cellular and molecular interactions that lead to inflammation and autoimmune diseases, such as psoriasis, psoriatic arthritis, and Sjögren's disease, in addition to RA and lupus.[916] To broaden this purview, scleroderma was added in FY24. Many NIH ICOs supported AMP AIM programs from FY22 to FY24, such as NIAMS, NIDCR, NEI, NIAID, ORWH, and OADR-ORWH. AMP AIM is using novel research tools to uncover cellular interactions that cause inflammation, injury, abnormal function, and clinical disease. The knowledge gained through these studies will lead to a better understanding of the biological processes that underlie autoimmune disorders and will facilitate development of more effective treatments.[917] For example, the Sjögren's Team for Accelerating Medicines Partnership aims to better understand the biology of, and ultimately improve care for, people with Sjögren's disease and other autoimmune-driven salivary gland conditions.[918]

In FY23 and FY24, NIH supported several research efforts to advance the study of autoimmune diseases and the exposome—the measure of all the environmental exposures across an individual lifetime and how those exposures affect biological processes and relate to health and disease. For example, the Exposome in Autoimmune Disease Collaborating Teams Planning Awards were launched in collaboration with OADR-ORWH and seven NIH ICOs to create a national interdisciplinary research network exploring the exposome in autoimmune diseases.[919] OADR-ORWH and NIAMS supported six awards. In addition, OADR-ORWH, in collaboration with NIEHS, NIAMS, NIA, NCI, and NINDS, supported the establishment of the Network for

[913] https://www.nih.gov/about-nih/impact-nih-research/improving-health/technology-patient-care#:~:text=Back-,Automatic%20Blood%20Counter,-Image
[914] Sparks R, et al. Nat Med. 2024 Sep;30(9):2461-2472. Epub 2024 Jul 3. PMID: 38961223.
[915] https://www.niaid.nih.gov/news-events/new-way-measure-and-predict-human-immune-health
[916] https://fnih.org/press-release/the-fnih-announces-transformative-partnership-to-identify-and-map-key-biological-pathways-that-drive-autoimmune-and-immune-mediated-diseases/
[917] https://www.niams.nih.gov/grants-funding/niams-supported-research-programs/accelerating-medicines-partnership-amp
[918] https://www.nidcr.nih.gov/news-events/nidcr-news/2023/turning-tap-back
[919] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-112.html

Exposomics in the U.S Coordinating Center.[920] The Center will support the integration of exposomics research across NIH, promoting interdisciplinary partnerships that seek to better understand how environmental factors impact health outcomes, including for autoimmune diseases.

Treatments and Interventions

Many of the medications that doctors prescribe to treat autoimmune diseases work to suppress or tamp down a patient's overactive immune system. These medications can effectively treat autoimmune diseases, but when used long-term—as is often the case because many autoimmune diseases are chronic conditions—they can also increase the risk of infections, cancers, severe birth defects, and miscarriage. Tapering off these medications once disease symptoms subside reduces these side effects while risking the potential for a disease flare up. In FY24, a NIAID-sponsored clinical trial evaluating people with stable systemic lupus erythematosus found that the risk for severe flare of lupus was low for both individuals who were tapered off long-term immunosuppressive therapy and those who continued taking their therapy.[921] Researchers hope that the results of this trial will help patients better understand the likelihood of a flare up after tapering off of treatment and help them make informed decisions about withdrawal of treatment based on individual circumstances and risk tolerance.[922] This clinical trial was conducted as a part of the NIAID Autoimmunity Centers of Excellence network, which forged a new collaboration with OADR-ORWH in FY24.[923,924] As a result of this collaboration, the network now includes a new center focused on endocrine-specific autoimmunity, along with five new pilot projects across the network. The network is designed to enable collaborative research in the search for innovative and effective treatments for autoimmune diseases.

From FY22 to FY24, NIH supported research to better treat a variety of autoimmune diseases, from the relatively common to the ultra-rare. For example, Sjögren's disease is a relatively common disorder, affecting 1 to 4 million people in the U.S. and causing reduced saliva production and dry mouth. While relatively common, Sjögren's remains poorly understood and difficult to treat. NIDCR researchers have been working to understand the mechanisms at play in this disorder and develop new therapeutic options for patients. In FY22 and FY23, researchers first identified the mechanism that results in increased salivary cell turnover in Sjögren's disease,[925] which enabled them to develop a gene therapy approach to restore salivary gland function in mice.[926] In FY24, a different group of researchers found that an FDA-approved drug for RA helped to regulate and reduce the aberrant immune response in salivary gland cells from Sjögren's patients.[927]

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[920] https://orwh.od.nih.gov/in-the-spotlight/all-articles/oadr-orwh-co-funds-newly-created-exposomics-coordinating-center
[921] Chakravarty EF, et al. Lancet Rheumatol. 2024 Mar;6(3):e168-e177. Epub 2024 Jan 29. PMID: 38301682.
[922] https://www.niaid.nih.gov/news-events/stable-lupus-tapering-immunosuppressant-low-flare-risk
[923] https://www.niaid.nih.gov/research/autoimmunity-centers-excellence
[924] https://www.autoimmunitycenters.org/
[925] Tanaka T, et al. Autophagy. 2022 Jul;18(7):1629-1647. Epub 2021 Nov 22. PMID: 34802379.
[926] Nakamura H, et al. Sci Rep. 2022 Nov 3;12(1):18570. PMID: 36329045.
[927] Gupta S, et al. Ann Rheum Dis. 2024 Jul 15;83(8):1034-1047. PMID: 38527764.

CHAPLE disease is a life-threatening, ultra-rare condition caused by overactivation of the complement arm of the immune system that works by enhancing the ability of antibodies and immune cells to clear microbes from the body. In FY23, the FDA approved the first and only treatment for CHAPLE disease after NIAID researchers and their collaborators demonstrated that this treatment was safe and effective in children and adults.[928,929] Researchers are hopeful that these research advances will lead to better treatments for patients with Sjögren's and CHAPLE diseases, among other autoimmune diseases and disorders.

Infectious Diseases and Countermeasures

Infectious diseases continue to pose a significant threat to human health, with many types of infections having far-reaching, global consequences—this is partly why infectious diseases and countermeasures are often discussed together. In addition to global spread of naturally occurring infectious diseases, the deliberate release of pathogenic agents—such as anthrax or smallpox—could cause large-scale public health emergencies. Infectious diseases have a wide variety of causes, including viruses, bacteria, fungi or yeasts, and parasites. In 2023, the CDC reported that two of the top 10 leading causes of death in the U.S. were infectious disease related: chronic lower respiratory disease (at fifth) and COVID-19 (at tenth). Also, in 2022 and 2023, the sixth leading cause of infant death in the U.S. was bacterial sepsis of the newborn.[930] NIH recognizes the need to transform the way we prevent, control, and treat infectious diseases with the intent of reducing negative global impact; and supports basic research, pre-clinical development, and clinical evaluation on infectious diseases and countermeasures.

Summary of NIH Activities

NIH conducts and supports research on infectious diseases and countermeasures, both through its extramural program, and at its own specialized intramural research laboratories. NIH's wide-ranging infectious disease and countermeasures portfolio includes research in vector-borne diseases such as those from mosquitos and ticks; major worldwide infectious diseases like HIV, malaria, tuberculosis, and viral hepatitis; and emerging and re-emerging infectious diseases and related concerns including influenza, COVID-19, Ebola, and antimicrobial resistance. NIH supports and conducts research to better understand, detect, prevent, and treat infectious diseases, as well as supporting countermeasures research resources and infrastructure.

Research on infectious diseases and countermeasures is primarily conducted and supported by NIAID, however, many other NIH ICOs also supported research in this area. From FY22 to FY24, NIH funding for infectious diseases research was $8.2 billion in FY22, $8.2 billion in FY23, and $8.0 billion in FY24.[931] NIH

[928] https://investor.regeneron.com/news-releases/news-release-details/veopoztm-pozelimab-bbfg-receives-fda-approval-first-treatment
[929] Ozen A, et al. Lancet. 2024 Feb 17;403(10427):645-656. Epub 2024 Jan 23. PMID: 38278170.
[930] https://www.cdc.gov/nchs/products/databriefs/db521.htm
[931] https://report.nih.gov/funding/categorical-spending#/

funding for biodefense and related countermeasures research was $3.1 billion in FY23 and $2.9 billion in FY24.[932]

Vector-Borne Disease Research

Vector-borne diseases (VBDs) are those transmitted by the bites of infected blood-feeding insects—like mosquitoes, ticks, and sandflies—which act as carriers of the disease. VBDs can be caused by various pathogens, including viruses, bacteria, and parasites. 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 VBDs, including tickborne diseases, and provide information on NIH actions with respect to tickborne diseases. In response to this mandate, Appendix C includes the following information on NIH actions in FY22, FY23, and FY24, regarding tickborne diseases and other VBDs: epidemiological, fundamental, translational, and clinical research updates; committees convened; programs active; and workshops held.

Infectious Diseases

NIH supports research to control and prevent diseases caused by virtually all human infectious agents. Major infectious diseases—such HIV, malaria, tuberculosis, and viral hepatitis—significantly impact the health and well-being of millions of people in the U.S. and around the world. NIH also supports research on many other infectious diseases that affect human health and wellbeing, such as Epstein-Barr Virus, respiratory syncytial virus, norovirus, tickborne diseases, mosquito-borne diseases, and fungal diseases. NIH conducts and supports research from basic to pre-clinical development to clinical trials to better understand, prevent, treat, and improve the quality of life of all people.

HIV/AIDS

The human immunodeficiency virus (HIV) can lead to infection that, if untreated, may progress to acquired immunodeficiency syndrome (AIDS), the most advanced stage of HIV disease. Largely because of years of NIH-supported research and investment, HIV has transformed from a fatal diagnosis to a manageable chronic disease. However, there remain barriers to management of HIV/AIDS, and infection with HIV continues to be a serious threat to a long, healthy lifespan. NIH supports a robust HIV research portfolio covering basic, translational, clinical, and implementation sciences, which requires a multi-ICO, interdisciplinary approach.

OAR provides scientific coordination and management of the NIH HIV research program. From FY22 to FY24, OAR participated in 12 public-facing community engagements, including listening sessions,[933]

[932] Beginning with FY23, NIH converted the Biodefense category to an automated category to enhance accuracy and better encompass research funding related to this topic. Since manual and automated figures are not comparable, the historical funding numbers for the manual category are only available upon request at rcdc@mail.nih.gov. Use of the Biodefense and Related Countermeasures RCDC category predates a recent transition in NIAID's mission and research priorities. While NIH will continue to support infectious disease research, specific research activities and mechanisms for budget estimates will change to align with NIH's new vision. These budget numbers are not representative of relevant activities for future work. RCDC funding is available here: https://report.nih.gov/funding/categorical-spending#/

[933] https://oar.nih.gov/news-and-events/oar-updates/new-release-hiv-partner-outreach-engagement-report

workshops,[934] and site visits with different groups and organizations to inform the next iteration of the NIH HIV research agenda, due for release in FY26.[935,936] NIH research also directly informs the five HHS-approved clinical guidelines for the treatment of HIV and related infections and HIV care during the perinatal period.[937] The guidelines are updated regularly by panels of clinical experts in HIV treatment and care who comprise working groups of the OAR Advisory Council. In FY23, the guidelines for breastfeeding were updated to reflect evidence that individuals with undetectable HIV viral loads can breastfeed with minimal risk of transmission.[938] In FY24, clinical guidelines to prevent cardiovascular disease were updated to include recommendations for statin therapy to prevent atherosclerotic cardiovascular disease in people with HIV aged 40 to 75 with low risk for the disease.[939] In FY24, new guidelines for anal cancer screening in people with HIV were published, recommending high-resolution anoscopy for people over 35 or with specific risk factors.[940]

To support the federal Ending the HIV Epidemic initiative, OAR coordinated 15 HHS-wide implementation research studies across regions disproportionately affected by HIV.[941] These projects leveraged national coordinating and regional research hubs to develop and evaluate innovative delivery strategies. Each project aligned with the initiative's four pillars—prevent, diagnose, treat, and respond—and applied rigorous methods to address key barriers in HIV care and prevention, and achieve an end to AIDS.

Unfortunately, stigma around HIV stops many from getting screened for the virus, which has an impact on its prevention and treatment, and the quality of life of people living with HIV. FIC, in collaboration with NCI, NICHD, NIDA, and NIMH, supported a funding opportunity for research to understand how to reduce stigma as a factor in HIV transmission, to eliminate or mitigate the aspects of stigma that limit beneficial health outcomes for the infected and vulnerable individuals and communities. It also included exploratory studies to determine the feasibility of stigma interventions related to HIV prevention, treatment and/or care in low and middle-income countries. During FY22 to FY24, this funding opportunity grew from small exploratory research projects to larger projects allowing more funds and time to carry out intervention trials.[942]

NIH support over decades has led to breakthrough advancements in medical interventions to prevent and treat HIV/AIDS, such as anti-retroviral therapy (ART) and pre-exposure prophylaxis (PrEP). PrEP is a standardized regimen for taking ART by people who do not have HIV that reduces the risk of getting HIV from sex by about 99 percent and from injection drug use by at least 74 percent. Finding ways to prevent HIV transmission during pregnancy are of utmost importance to the mother and infant's health. Pregnant

[934] https://oar.nih.gov/nih-virtual-workshop-community-voices-2023/executive-summary
[935] https://oar.nih.gov/news-and-events/events
[936] https://oar.nih.gov/hiv-policy-and-research/strategic-plan
[937] https://clinicalinfo.hiv.gov/en/guidelines
[938] https://oar.nih.gov/news-and-updates/oar-updates/update-clinical-guidelines-infant-feeding-supports-shared-decision-making
[939] https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/statin-therapy-people-hiv?view=full
[940] https://www.oar.nih.gov/update-clinical-guidelines-high-resolution-anoscopy-anal-cancer-screening
[941] https://www.cdc.gov/ehe/php/about/goals.html
[942] https://www.fic.nih.gov/Programs/Pages/stigma-hiv-aids.aspx

women are estimated to be three times more likely to acquire HIV through sexual intercourse than similarly aged women who are not pregnant, and HIV can be transmitted perinatally during pregnancy, childbirth, or breastfeeding. In FY24, a clinical study supported by NIAID, NICHD, and NIMH demonstrated that two different HIV prevention methods using either an ART vaginal ring or oral PrEP were safe for use during pregnancy and showed no difference in pregnancy outcomes as compared to historical data.[943] Vaccines are another promising, but still unavailable, tool in the toolbox to prevent HIV transmission. In FY23, NIAID supported a Phase 1 clinical trial to evaluate the safety and efficacy of a novel preventive HIV vaccine candidate, VIR-1388, in the U.S. and South Africa.[944]

In addition to ART, researchers are also exploring microbicides—experimental products that could be applied topically and act locally at the initial site of HIV exposure—to safely prevent HIV acquisition. A large clinical study found that two HIV prevention methods, the monthly dapivirine vaginal ring and daily oral PrEP, are each safe and effective for HIV prevention throughout pregnancy.[945,946] The dapivirine ring is made of flexible silicone and continuously releases the antiretroviral drug dapivirine, and the oral PrEP was a combination of the drugs tenofovir disoproxil fumarate and emtricitabine. The study focused on women who began using the ring or oral PrEP in their second trimester. Pregnancy and birth outcomes were similar to those seen in the general population, and no HIV acquisitions occurred among participants. The trial was conducted by the Microbicide Trials Network, an international research network funded by NIAID, with co-funding from NICHD and NIMH.

Daily oral ART is effective for managing HIV, but many people struggle with taking daily pills due to various barriers, including mental health disorders, housing insecurity, and substance use. Research supported by NIMH and NIAID shows that long-acting injectable medications, administered every 4 or 8 weeks, could be a more accessible option for those facing difficulties taking daily pills.[947] Among 133 study participants, those already controlling their HIV with pills maintained their viral suppression with the injections. Impressively, most patients with uncontrolled HIV before starting injections also achieved viral suppression quickly. These findings suggest that long-acting injections could be a promising treatment option for people with HIV, especially those who have historically had less access to ART.

Managing treatment for HIV and HIV-associated co-occurring conditions (other co-occurring diseases, conditions, coinfections, or complications) requires complex interventions. Today, people living with HIV typically must take ART daily—a regimen usually of three or more medicines—to stay healthy and prevent transmission of the virus to others. An HIV cure in the classic sense would require the elimination of the reservoir of all virus-carrying cells. These cells, which contain HIV DNA, have entered a resting state such that they do not produce any parts of the virus unless they become activated. HIV reservoir cells can survive in this resting state for years, even for life, while remaining invisible to the immune system and

[943] https://www.niaid.nih.gov/news-events/vaginal-ring-and-oral-pre-exposure-prophylaxis-found-safe-hiv-prevention-throughout
[944] https://www.niaid.nih.gov/news-events/clinical-trial-hiv-vaccine-begins-united-states-and-south-africa
[945] https://www.clinicaltrials.gov/study/NCT03965923
[946]https://www.niaid.nih.gov/news-events/vaginal-ring-and-oral-pre-exposure-prophylaxis-found-safe-hiv-prevention-throughout
[947] Gandhi M, et al. Ann Intern Med. 2023 Jul;176(7):969-974. Epub 2023 Jul 4. PMID: 37399555.

antiretroviral drugs. An alternative to a classic cure is sustained ART-free remission. This objective would not involve eradicating the HIV reservoir, but rather would allow a person living with HIV to keep latent virus suppressed without medication.

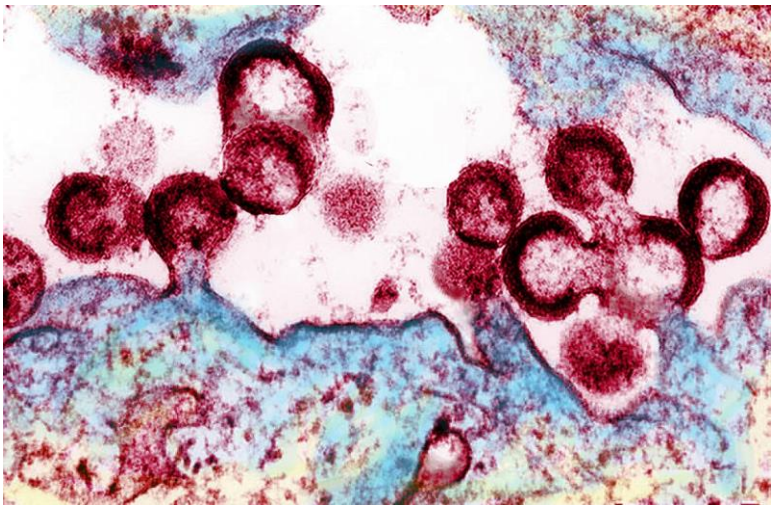


Figure 39. When a resting immune cell that is latently infected with HIV gets reactivated, the cell starts producing HIV virions (red) that bud and release from the cell (blue). Credit: NIAID/NIH

Achieving sustained remission of HIV without life-long ART is a top HIV research priority for NIH. In FY22, NIAID researchers identified two distinct ways that the immune system in people with HIV can control the virus for an extended period after stopping ART under medical supervision.[948] Also in FY22, researchers supported by the International Maternal Pediatric Adolescent AIDS Clinical Trial Network documented the third known case of HIV remission after the patient received a stem cell transplant for treatment of a type of leukemia.[949] Finally, in FY24, another group of researchers supported by the network reported that four children who started ART shortly after birth remained free of detectable HIV for more than one year after their ART was paused.[950] This work underscores the potential of early interventions in newborns to limit viral reservoir formation. The network is funded by NIAID, NICHD, and NIMH. Taken together, these studies contribute to growing body of knowledge on how to achieve HIV remission.

HIV causes many health issues other than AIDS that are not improved by ART. HIV treatment also may lead to harmful side effects, interactions with other medications, HIV drug resistance, and other complications. Another of NIH's top priorities is to improve the health outcomes of people with HIV by addressing these comorbidities along with the other infections and complications faced by people with HIV. From FY22 to FY24, FIC supported locally relevant research projects to stimulate new research on the interplay between HIV and development of comorbidities and complications not due to infections in people living with HIV.

[948] Blazkova J, et al. Nat Med. 2021 Nov;27(11):1893-1898. Epub 2021 Oct 28. PMID: 34711975.
[949] https://www.niaid.nih.gov/news-events/researchers-document-third-known-case-hiv-remission-involving-stem-cell-transplant
[950] https://www.niaid.nih.gov/news-events/children-surpass-year-hiv-remission

NIH hopes that this work will lead to new strategies for effective diagnosis, prevention, therapeutic intervention, and integrated clinical care for people living with HIV experiencing comorbid conditions.[951]

Diabetes is a common comorbidity alongside many other diseases or conditions, including HIV. NIAID-supported researchers demonstrated in a Phase 2b study that weekly injections of semaglutide (an anti-diabetic medication) were safe and led to a 31 percent reduction in liver fat among people with HIV and metabolic dysfunction-associated steatotic liver disease.[952] The study was the first to explore semaglutide's effects on this common liver disease in HIV-positive individuals. Participants, whose HIV was managed with ART, showed additional health benefits such as weight loss and improved blood glucose and triglyceride levels. The research, conducted in the U.S. and Brazil, suggests semaglutide could be a promising therapy for improving liver health in people living with HIV, with further studies underway to explore associated immunologic and inflammatory responses.

Malaria

Malaria is a mosquito-borne infectious disease caused by the bite of female *Anopheles* mosquitoes, which spread infectious *Plasmodium* parasites into a host. Traditional malaria symptoms include fever, chills, headache, muscle aches, and fatigue. Nausea, vomiting, and diarrhea are also common, and untreated malaria can lead to severe disease, kidney failure, and death. Neurological complications can occur in severe cases, most commonly in young children. NIAID is the lead IC investigating the disease, supporting a wide range of research including on vaccines and preventive interventions, mosquito control techniques, easy-to-use diagnostics, and improved therapies as parasites continue to develop resistance to currently available antimalarials.

Two vaccines to prevent malaria are available; however, their variable efficacy underscores the need for new interventions that offer high-level protection against disease. In FY24, two NIAID-supported clinical trials demonstrated that a vaccine candidate (PfSPZ) was safe and well-tolerated in healthy adults and women anticipating pregnancy in malaria endemic areas.[953] The studies showed that the vaccine candidate, given together with antimalarial treatment prior to vaccination, conferred a significant degree of protection from parasite infection and clinical malaria that was sustained over a span of two years without the need for a booster dose—a first for any malaria vaccine. The findings will need to be confirmed through additional clinical trials, but the approach modeled in this study could open improved ways to prevent malaria in pregnancy.

Antibodies are another promising avenue for malaria prevention, which work by neutralizing the parasites in the skin and blood before they can infect liver cells. From FY22 to FY24, two NIAID clinical trials demonstrated monoclonal antibodies were efficacious in preventing malaria. The first clinical trial found that a single dose of a monoclonal antibody (CIS43LS) was up to 88.2 percent efficacious in preventing malaria in healthy adults in Mali.[954] Building on those results, a Phase 1 trial in the U.S. showed that

[951] https://www.fic.nih.gov/Programs/Pages/hiv-noncommunicable-diseases-ncds-lmics.aspx
[952] https://www.niaid.nih.gov/news-events/semaglutide-reduces-severity-common-liver-disease-people-hiv
[953] Diawara H, et al. Lancet Infect Dis. 2024 Dec;24(12):1366-1382. Epub 2024 Aug 14. PMID: 39153490.
[954] Kayentao K, et al. N Engl J Med. 2022 Nov 17;387(20):1833-1842. Epub 2022 Oct 31. PMID: 36317783.

another monoclonal antibody (L9LS) provided 88 percent protection in adults,[955] and a mid-stage trial of the same antibody in Mali found it to be 77 percent efficacious in children.[956] These findings suggest that monoclonal antibodies like CIS43LS and L9LS could offer long-lasting, single-dose preventive measures against malaria, with ongoing trials in Kenya and Mali to further assess whether they are efficacious in high-risk populations.

Tuberculosis

Tuberculosis (TB) is the leading infectious cause of death worldwide. Over the past 200 years, TB has claimed the lives of more than one billion people—more deaths than from malaria, influenza, smallpox, HIV/AIDS, cholera, and plague combined. Although TB treatment exists, drug resistance is a continued threat.

On World TB Day 2024, NIAID reaffirmed NIH's commitment to ending the TB pandemic while honoring those lives lost to TB disease.[957] NIAID supports and conducts basic, translational and clinical research to better understand TB and expedite the development of innovative new tools and strategies to improve diagnosis, prevention and treatment. To guide this work, in FY24, NIAID released its *2024 Strategic Plan for Tuberculosis Research*, an update to the first plan issued in 2018.[958] The updated plan has four strategic priorities: improving fundamental TB knowledge; advancing research to improve TB diagnosis; accelerating research to improve TB vaccine development; and, supporting research to advance strategies to treat and prevent TB.

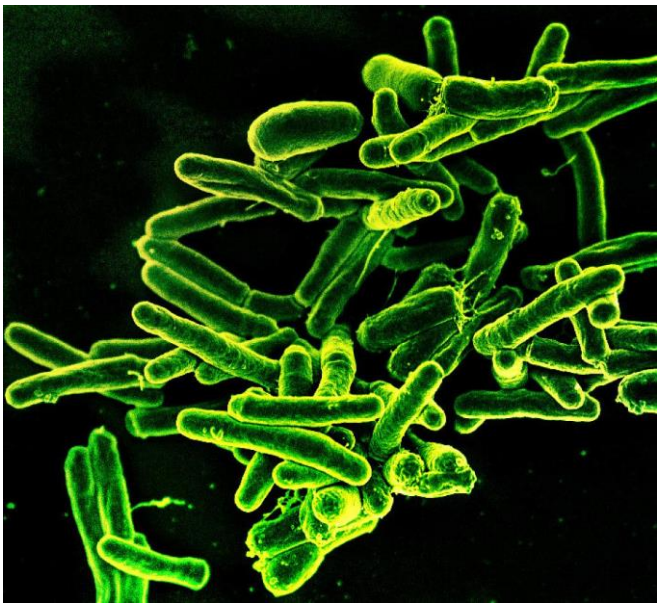


Figure 40. Scanning electron micrograph of the Mycobacterium tuberculosis bacteria, which cause TB. Credit: NIAID/NIH

[955] Wu RL, et al. N Engl J Med. 2022 Aug 4;387(5):397-407. PMID: 35921449.
[956] Kayentao K, et al. N Engl J Med. 2024 May 2;390(17):1549-1559. Epub 2024 Apr 26. PMID: 38669354.
[957] https://www.niaid.nih.gov/news-events/world-tb-day-2024-yes-we-can-end-tb
[958] https://www.niaid.nih.gov/sites/default/files/tb-strategic-plan-2024.pdf

In FY24, NIAID awarded funding for the Consortium for Design of TB Drug Regimens program to systematically refine preclinical models using relevant pre-clinical and clinical data, and provide the results from optimized models to identify the most efficacious combination regimens for future clinical testing through model-informed research.[959] One of the awarded projects was the Preclinical Design and Clinical Translation of TB Regimens Consortium, which established a multidisciplinary consortium of scientific leaders, drug developers, and other stakeholders to comprehensively assess evolving preclinical research challenges and opportunities. Their goal is to identify novel drug regimens that have the greatest potential for clinical success in adults and children with TB.[960]

In FY23, a NIAID-supported clinical trial testing a freeze-dried, temperature-stable experimental TB vaccine in healthy adults found that it was safe and stimulated both antibodies and cellular immune responses.[961] This trial was the first of its kind for a freeze-dried, thermostable TB vaccine. This is notable because the freeze-dried formulation does not require refrigeration and is mixed with sterile water just prior to injection. Thermostable vaccines are desirable in settings where maintaining cold or frozen vaccines for long periods can be costly and difficult.

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.

In FY22, NIH released its updated *Strategic Plan for NIH Research to Cure Hepatitis B*, a roadmap for ending the hepatitis B epidemic, focused on developing a cure as well as improved strategies for vaccination, screening, and follow-up care.[962] The revised plan incorporates lessons from the COVID-19 pandemic and recent advances in technology. The plan aligns with *HHS' Viral Hepatitis National Strategic Plan* and is designed to be a part of the agency's ongoing response to the effects of this disease.[963] The updated strategy focuses on understanding hepatitis B biology, developing tools and resources for fighting the virus, and creating strategies for its cure and prevention. The strategic planning efforts were led by NIAID in collaboration with various NIH ICs and emphasizes the importance of partnerships and advanced technologies to drive significant progress in combating hepatitis B.

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. No vaccine is currently available, so early diagnosis and treatment is the only means to prevent liver damage. In FY22, NIAID-supported researchers launched a research project to design a vaccine to combat the virus that causes Hepatitis C. This five-year award (contingent on availability of funds) will support a multidisciplinary research team across two universities and the National Institute of Standards

[959] https://grants.nih.gov/grants/guide/rfa-files/rfa-ai-22-059.html
[960] https://reporter.nih.gov/search/2FU90rwXJE-BaxkYj1Oq4Q/project-details/10782298
[961] Sagawa ZK, et al. Nat Commun. 2023 Mar 6;14(1):1138. PMID: 36878897.
[962] https://www.niaid.nih.gov/news-events/nih-updates-hepatitis-b-strategic-research-plan
[963] https://www.hhs.gov/hepatitis/viral-hepatitis-national-strategic-plan/index.html

and Technology. The researchers aim to develop a vaccine to induce broadly neutralizing antibodies and long-term memory T cell responses to help prevent Hepatitis C infection.

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a widespread human virus responsible for infectious mononucleosis and is linked to certain cancers and autoimmune diseases. It is one of the most common human viruses, so investigating better ways to prevent and reduce infection is important for improving the health of all.

In FY22, NIAID initiated an early-stage clinical trial to evaluate a preventive vaccine for EBV.[964] The trial aims to test the safety and immune response of a novel EBV vaccine in 40 healthy volunteer adults. This research effort represents a significant step in developing EBV vaccination options, potentially reducing the prevalence of associated diseases.

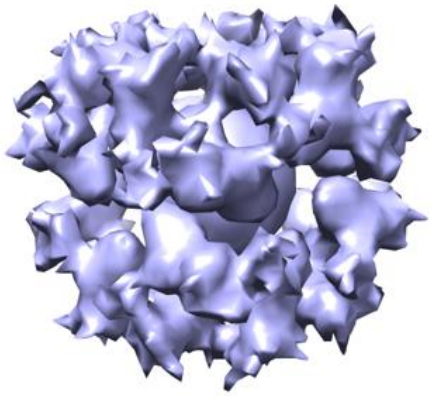


Figure 41. A CryoEM image of a candidate Epstein-Barr virus vaccine. Credit: NIAID/NIH

In FY23, a team of scientists from NIAID, in collaboration with the Walter Reed Army Institute of Research, conducted a study using investigational monoclonal antibodies targeting EBV. In laboratory settings, these antibodies were successful in blocking EBV infection in human cells, specifically targeting two key proteins on the virus's surface.[965] One of the antibodies, 769B10, provided near-total protection against EBV infection and lymphoma in mice. The findings suggest that these antibodies could serve as potential vaccine candidates or treatments for EBV infections, particularly for immunocompromised individuals. Further research on the antibody 769B10 is planned to explore its effectiveness.

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. Although this common virus typically causes mild, cold-like symptoms that resolve within a week, it can be deadly to older adults, children younger than 5 years old, people with chronic heart or lung disease, or weakened immune systems.

[964] https://www.niaid.nih.gov/news-events/nih-launches-clinical-trial-epstein-barr-virus-vaccine
[965] Chen WH, et al. Immunity. 2022 Nov 8;55(11):2135-2148.e6. Epub 2022 Oct 27. PMID: 36306784.

The first three RSV vaccines were approved by the FDA for use in the U.S. in FY23 and FY24, representing a significant public health achievement thanks to decades of American taxpayer-funded scientific discovery and research at NIH. These vaccines are largely based on a specific protein technology developed by NIAID scientists.[966,967] In FY23, the FDA approved the first RSV vaccine, Arexvy, for those aged 60 years and above, demonstrating more than 80 percent effectiveness in preventing symptomatic RSV lower respiratory tract infections.[968] Also in FY23, the FDA approved Abrysvo, which effectively combats RSV for older adults and was later approved as a maternal vaccine to protect infants from severe RSV-associated outcomes.[969] Finally in FY24, the FDA approved the mRNA vaccine mRESVIA, which protects individuals 50 years and older with similar efficacy to Arexvy.[970]

Norovirus

Norovirus is a highly infectious virus that is the leading cause of diarrhea and vomiting in the U.S. Norovirus commonly spread through food or water that is contaminated during preparation or through contaminated surfaces, but can also spread through close contact with a person who has norovirus infection. Norovirus has no approved therapeutics or vaccines to prevent its miserable effects.

The absence of approved norovirus therapeutics or vaccines is partly due to a lack of reliable research models to study norovirus infection and predict how effective interventions would be in people. In FY24, NIAID researchers developed the first animal model for human norovirus infection, which will provide researchers with a reliable model that can be used to determine which vaccines and therapeutics against norovirus are the best candidates for human clinical trials.[971]

Lyme Disease

Lyme disease is caused by a bacterium, *Borrelia burgdorferi* (and related species) that is transmitted by the bite of an infected tick. Most cases of Lyme disease can be effectively treated with oral antibiotics. However, some patients suffer from symptoms that linger long after the initial course of antibiotics, even though the active infection appears to be gone. Post-treatment Lyme Disease Syndrome (PTLDS) consists of lingering symptoms such as pain, fatigue, and cognitive difficulties or "brain fog," which linger following standard treatment for Lyme disease.

The cause of PTLDS remains unclear, though it may involve an immune response or underlying persistent infection. In FY23, NIAID allocated funding for five research projects to better understand the diagnosis and treatment of PTLDS. Research topics include: the role of peptidoglycan fragments (components of bacteria's protective cell membrane) in Lyme disease symptoms; immune biomarkers to predict Lyme disease progression and recovery; auto-antibodies as predictive markers for PTLDS; factors influencing

[966] https://www.niaid.nih.gov/news-events/nih-celebrates-fda-approval-rsv-vaccine-people-60-years-age-and-older
[967] https://www.niaid.nih.gov/diseases-conditions/safe-and-effective-rsv-protein-vaccines
[968] https://www.fda.gov/vaccines-blood-biologics/arexvy
[969] https://www.fda.gov/vaccines-blood-biologics/abrysvo
[970] https://www.fda.gov/vaccines-blood-biologics/vaccines/mresvia
[971] Rimkute I, et al. Nat Microbiol. 2024 Mar;9(3):877. Erratum for: Nat Microbiol. 2024 Mar;9(3):776-786. PMID: 38360987.

post-treatment Lyme disease outcomes; and using SI to identify early biomarkers for PTLDS risk. Findings from these studies could potentially benefit other chronic conditions like Long COVID and ME/CFS.[972]



Figure 42. This image shows how the design of the tick mouth makes ticks generally difficult to remove once they've attached for a blood meal. Credit: NIAID/NIH

Equine Encephalitis Viruses

Spread by mosquitos, alphaviruses primarily affect people in one of two ways: causing severe neurological impairment such as encephalitis (brain swelling) or crippling muscle pain similar to arthritis. Western, eastern, and Venezuelan equine encephalitis viruses are examples of those that cause brain swelling, while chikungunya and Ross River viruses are examples of those that cause crippling muscle pain. Under certain laboratory conditions, the viruses can transmit through the air by aerosol droplets and cause infection in humans and are therefore classified as priority pathogens, potential biological agents that pose a risk to national security and public health.[973]

In FY22, NIAID published the results from a 2019 Phase 1 clinical trial demonstrating that a vaccine candidate for equine encephalitis viruses is safe, well-tolerated, and induces a neutralizing antibody response in adult volunteers.[974] The vaccine uses virus-like particles to prompt immune responses without containing viral genetic material. The study supports further clinical evaluation and has led to a commercialization license agreement with a small drug company for continued development. In FY23, NIAID researchers identified SKT05, an antibody derived from macaques vaccinated with virus-like particles representing three encephalitic alphaviruses.[975] They demonstrated that these antibodies protected not only against infection in animal models with encephalitic alphaviruses, but also the alphaviruses that cause arthritis-like symptoms, including Chikungunya and Ross River virus.[976] Further

[972] https://www.niaid.nih.gov/news-events/nih-awards-will-fund-post-treatment-lyme-disease-syndrome-research
[973] https://www.niaid.nih.gov/research/niaid-biodefense-pathogens
[974] Coates EE, et al. Lancet Infect Dis. 2022 Aug;22(8):1210-1220. Epub 2022 May 11. PMID: 35568049.
[975] Sutton MS, et al. Cell. 2023 Jun 8;186(12):2672-2689.e25. Epub 2023 Jun 8. PMID: 37295404.
[976] https://www.niaid.nih.gov/news-events/alphaviruses

studies are planned to investigate potential clinical development of SKT05. They aim to better define how SKT05 interacts with viruses and whether it can confer protective benefits against additional alphaviruses.

Fungal Diseases

The world of fungi includes a wide range of organisms, such as mushrooms, molds, and yeast, that are common outdoors in water, soil, and air; indoors on surfaces; and on our skin and inside our bodies. Although many fungi are helpful—or even delicious, like edible mushrooms—there are many others which can cause disease. Some fungal infections are more common in people with weakened immune systems or hospitalized individuals, while other fungal infections can infect anyone, including otherwise healthy people. According to the CDC, more than one billion people worldwide get a fungal infection each year.[977]

Many NIH ICs conduct and support research to understand how fungal pathogens cause disease and develop new methods for diagnosing and treating fungal infections. In FY22, NIAID announced three awards to establish a network of Coccidioidomycosis Collaborative Research Centers to conduct research on coccidioidomycosis, also known as Valley Fever.[978] Symptoms resemble community-acquired pneumonia (e.g., fever, cough, shortness of breath) caused by bacteria or viral organisms and generally resolve on their own. These multi-disciplinary research teams will collaborate to investigate potential diagnostics, therapeutics, and vaccines for this fungal disease, which primarily affects regions in the southwestern U.S., Mexico, and Central and South America.

In FY24, a team of NIH Clinical Center, NHLBI, and NIAID researchers developed and tested a new imaging method that allows for specific detection of *Aspergillus fumigatus* fungal infections in a timely manner without the need for invasive procedures.[979] *A. fumigatus* is widespread in nature and generally only causes disease in individuals with an immunodeficiency. The method uses a first-of-its-kind radioactive tag that enables fungal infections to be seen in mice models using a specialized PET scanner for small animals.[980,981] The method is currently being translated to human use, and may be able to be used for monitoring responses to treatment as well as initial diagnosis. Also, in FY24, a different team of NIH Clinical Center, NCI, and NIAID researchers and their colleagues demonstrated that a newly identified mold species, *Mucor germinans*—which also generally only causes disease in people with a compromised immune system—produces structures that can be used as an effective marker to distinguish mucormycosis from other fungi. This discovery will enable faster diagnoses and more timely clinical management.[982]

Emerging Infectious Diseases and Countermeasures

The emergence of new pathogens—such as SARS-CoV-2, the virus that causes COVID-19— and the periodic re-emergence of pathogens like Ebola, require NIH and the biomedical and behavioral research community to be vigilant and able to pivot as needed to address emerging infectious diseases. NIH also funds research on other, less well-known emerging infectious diseases and infectious agents, such as mammal borne

[977] https://www.cdc.gov/fungal/about/index.html
[978] https://www.niaid.nih.gov/news-events/nih-supports-valley-fever-research-new-awards
[979] https://nihrecord.nih.gov/2024/09/13/nih-develops-imaging-method-detect-fungal-infection
[980] Shah S, et al. Sci Transl Med. 2024 Aug 14;16(760):eadl5934. Epub 2024 Aug 14. PMID: 39141701.
[981] Basuli F, et al. J Labelled Comp Radiopharm. 2024 Jul;67(9):308-313. Epub 2024 Jul 9. PMID: 38982015.
[982] Li N, et al. mBio. 2024 Aug 14;15(8):e0014424. Epub 2024 Jul 2. PMID: 38953355.

viruses and those with unknown etiology. Our society is increasingly global, and efforts to combat infectious diseases and bolster countermeasures require coordination that goes beyond geographic boundaries.

Influenza

Seasonal influenza, or flu, is a highly contagious respiratory illness caused by influenza viruses that infect the nose, throat and lungs. Each year, influenza causes millions of illnesses worldwide and, in the U.S., results in thousands of hospitalizations and deaths. Influenza is especially dangerous for people 65 years and older, young children and people with certain health conditions, such as heart disease or asthma. There are four types of influenza virus: types A, B, C, and D. Aquatic birds are the primary source of type A, which is also widespread in various mammals, including humans and pigs. Influenza B virus and influenza C virus primarily infect humans, and influenza D virus is found in cattle and pigs. An influenza pandemic occurs when a new influenza virus emerges that is able to infect and spread easily from person to person and to which most of the global population does not have immunity.

NIH conducts and supports research to find new and improved ways to prevent seasonal influenza and novel influenza viruses with pandemic potential, strengthening existing approaches to protecting the public health. In FY22, NIAID researchers started clinical testing of a novel influenza vaccine, BPL-1357, at the NIH Clinical Center.[983] Developed by NIAID researchers, BPL-1357 is a whole-virus vaccine comprising four strains of inactivated avian flu viruses. The trial emphasizes the potential of BPL-1357 to induce universal influenza immunity, including mucosal immunity, which could provide broader protection against various influenza strains. In FY23, a clinical trial using an mRNA platform for an experimental universal influenza vaccine developed by NIAID researchers began enrolling volunteers. The Phase 1 trial is testing the experimental vaccine, known as H1ssF-3928 mRNA-LNP, for safety and its ability to induce an immune response. A similar protein-based vaccine developed by NIAID researchers was previously tested in early clinical trials with positive results. Researchers aim to compare the new vaccine's effectiveness and safety with existing flu vaccines, with follow-up evaluations extending up to one-year post-vaccination.[984]

There are two proteins found on the surface of the influenza virus: hemagglutinin and neuraminidase. Hemagglutinin enables the flu virus to enter a human cell and initiate infection, while neuraminidase allows newly formed viruses to exit the host cell and multiply throughout the body. These proteins can combine in different ways to create an assortment of influenza virus strains, such as H1N1 and H5N1, among others. In FY23, NIAID researchers showed in animal models that immunization with a specific piece of hemagglutinin intact and another piece removed, resulted in a broader influenza-specific response.[985] To test whether this would work in humans, NIAID researchers conducted first-in-human Phase 1 clinical trials with vaccines targeting two different types of hemagglutinin.[986,987,988] Both were safe, immunogenic, and induced a broadly neutralizing antibody response. These novel immunogens have the

[983] https://www.niaid.nih.gov/news-events/trial-potential-universal-flu-vaccine-opens-nih-clinical-center
[984] https://www.niaid.nih.gov/news-events/clinical-trial-mrna-universal-influenza-vaccine-candidate-begins
[985] Widge AT, et al. Sci Transl Med. 2023 Apr 19;15(692):eade4790. Epub 2023 Apr 19. PMID: 37075129.
[986] Andrews SF, et al. Sci Transl Med. 2023 Apr 19;15(692):eade4976. Epub 2023 Apr 19. PMID: 37075126.
[987] Casazza JP, et al. NPJ Vaccines. 2024 Sep 17;9(1):171. PMID: 39289377.
[988] Mantus GE, et al. Sci Transl Med. 2025 Jan;17(779):eadr8373. Epub 2025 Jan 1. PMID: 39742506.

potential to provide broad protection that would be especially important in the advent of a pandemic with novel influenza subtypes.

Avian Influenza

Avian influenza, also known as avian flu or bird flu, is a disease caused by the influenza A virus. Because it primarily affects birds, when it does obtain the ability to infect humans, it can result in more serious illness due to a lack of pre-existing human immunity. Since 2003, H5N1 influenza viruses have circulated in 23 countries, mainly affecting wild birds and poultry with about 900 human cases, primarily among people who have had close contact with infected birds. In the past few years, however, a highly pathogenic avian influenza (HPAI) virus called H5N1 has spread to infect more than 50 animal species, and in FY24, the U.S. reported a viral outbreak among dairy cows in Texas. Although the virus has so far shown no genetic evidence of acquiring the ability to spread from person-to-person, public health officials are closely monitoring the dairy cow situation as part of overarching pandemic preparedness efforts.

In FY24, NIAID researchers and collaborators worked quickly to characterize HPAI H5N1 infection and transmission in dairy cows to better understand the risk to human health. Studies conducted by different teams of researchers suggested that milk and milking procedures could be primary routes of transmission in dairy cows, which was confirmed by detection of high viral RNA levels in milk.[989,990] A group of NIAID-supported researchers revealed that both H5N1 and H1N1 highly pathogenic influenza viruses remained infectious in unpasteurized milk and on milking equipment materials for several hours.[991] Finally, concurrent studies conducted and supported by NIAID indicated that high H5N1 influenza levels were found in mice given raw milk from infected dairy cows.[992] The studies also showed that heating the infected milk significantly reduced levels of H5N1 influenza, though traces remained after brief pasteurization when initial virus levels in raw milk were high.[993] Taken together, these findings highlight the risk for H5N1 virus transmission to humans from contaminated surfaces and milk during the milking process and for hours after its completed. They also demonstrate NIH's ability to rapidly respond to emerging public health threats to better understand the risk to human health.

COVID-19

Coronaviruses are a large family of viruses that usually cause mild to moderate upper-respiratory tract illnesses in humans. However, three coronaviruses have caused more serious and fatal disease in people: SARS coronavirus (SARS-CoV), which emerged in November 2002 and causes severe acute respiratory syndrome (SARS); MERS coronavirus (MERS-CoV), which emerged in 2012 and causes Middle East respiratory syndrome (MERS); and SARS-CoV-2, which emerged in 2019 and causes coronavirus disease 2019 (COVID-19). NIH continues to conduct and support basic research to understand how coronaviruses infect cells and causes disease and what interventions can detect, prevent and stop the spread of disease.

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[989] Halwe NJ, et al. Nature. 2025 Jan;637(8047):903-912. Epub 2024 Sep 25. PMID: 39321846.
[990] Baker AL, et al. Nature. 2025 Jan;637(8047):913-920. Epub 2024 Oct 15. PMID: 39406346.
[991] Le Sage V, et al. Emerg Infect Dis. 2024 Aug;30(8):1721-1723. Epub 2024 Jun 24. PMID: 38914418.
[992] Guan L, et al. N Engl J Med. 2024 Jul 4;391(1):87-90. Epub 2024 May 24. PMID: 38785313.
[993] Kaiser F, et al. N Engl J Med. 2024 Jul 4;391(1):90-92. Epub 2024 Jun 14. PMID: 38875103.

NIAID researchers evaluated differences between adults and children with SARS-CoV-2 infection, and compared those differences to cases of multisystem inflammatory syndrome in children, a rare and severe condition associated with COVID-19 where different body parts can become inflamed.[994] One study found that infants and young children infected with SARS-CoV-2 had a strong, sustained antibody response and high levels of inflammatory proteins in the nose, but not in the blood, unlike adults. This suggests a localized immune response that helps control the virus at the entry point and results in milder disease.[995] A related study by NIAID researchers further demonstrated that children have stronger innate immune responses to SARS-CoV-2 compared to adults, with early increased levels of several inflammatory biomarkers in children with multisystem inflammatory syndrome, which are generally higher and qualitatively distinct from those in children with COVID-19.[996] These findings suggest potential strategies for developing vaccines with immune boosters that could mimic this protective response without causing harmful inflammation, and also highlight the genetic susceptibility of some children to multisystem inflammatory syndrome.

Rapid diagnostic tools and vaccines remain vital to NIH's public health toolbox as SARS-CoV-2 continues to evolve and multiple respiratory viruses circulate throughout the year and cause people to feel sick. Rapid diagnostics can help guide public health responses and inform patient treatment. Currently, there are two main approaches to testing—quick at home antibody-based tests and slower nucleic acid (DNA or RNA) amplification tests performed in clinical laboratories. In FY22, NIAID-supported researchers showed that the microfluidic Combinatorial Arrayed Reactions for Multiplexed Evaluation of Nucleic acids test can be used for the clinical detection of nine respiratory viruses, enabling rapid detection of SARS-CoV-2 variants versus influenza A.[997]

Mucosal vaccines are a type of immunization administered through mucosal surfaces, such as those in the nose or mouth, to stimulate an immune response at these entry points, where many pathogens enter the body. In FY23, NIAID co-hosted a virtual workshop to address the development of mucosal vaccines for SARS-CoV-2, which could potentially block transmission and infection more effectively than current vaccines. The workshop highlighted the need to understand correlates of protection, for improved animal models, and called for careful clinical design.[998] Building on this, in FY24, a Phase 1 trial began enrolling participants to test the safety of an experimental nasal vaccine designed to provide enhanced protection against emerging variants of SARS-CoV-2.[999] This trial aims to develop next-generation COVID-19 vaccines that could reduce infections and transmission by generating robust mucosal immunity.

Ebola Virus Disease

Ebola is a serious and often fatal illness caused by several viruses, including Ebola virus and Sudan virus. The Ebola virus is zoonotic in nature, with its natural reservoir being animals like bats. It intermittently

[994] https://www.niaid.nih.gov/news-events/mis-c-blog
[995] Wimmers F, et al. Cell. 2023 Oct 12;186(21):4632-4651.e23. Epub 2023 Sep 29. PMID: 37776858.
[996] Sacco K, et al. Nat Med. 2022 May;28(5):1050-1062. Epub 2022 Feb 17. PMID: 35177862.
[997] Welch NL, et al. Nat Med. 2022 May;28(5):1083-1094. Epub 2022 Feb 7. Erratum in: Nat Med. 2024 Jan;30(1):307. PMID: 35130561.
[998] Knisely JM, et al. NPJ Vaccines. 2023 Apr 12;8(1):53. PMID: 37045860.
[999] https://www.niaid.nih.gov/news-events/nih-sponsored-trial-nasal-covid-19-vaccine-opens

triggers human outbreaks when transmitted from these hosts. Symptoms of Ebola include fever, headache, muscle pain, weakness, fatigue, diarrhea, vomiting, stomach pain, and severe bleeding and bruising.

The first vaccine for Ebola virus, rVSV-ZEBOV, which was developed with assistance from NIAID, was approved in the U.S. in FY20. This vaccine and others can now be used to protect people in high-risk areas, or people who have had contact with sick Ebola disease patients. In FY23, two randomized, placebo-controlled clinical trials evaluated three different administration strategies for rVSV-ZEBOV in adults and children, and found all regimens to be safe and effective at producing antibodies.[1000] Antibody responses were detected as early as 14 days after the first vaccination and persisted for up to a year. This finding is notable because vaccines against Ebola disease are typically administered during an outbreak and so information about how rapidly a vaccine produces an antibody effect is of potential use in efforts to protect at-risk populations. However, it is not currently known what level of antibody response reliably correlates with protection against Ebola virus infection or disease. As no participants contracted Ebola during the trials, the investigators were not able to assess protection from disease. These results led to the FDA approving an expanded indication for rVSV-ZEBOV in individuals 12 months of age and older (previously approved for individuals 18 years of age and older).[1001]

Because Ebola disease can be caused by different viruses, it is important to design vaccines that provide protection against other viruses that can cause Ebola, such as Sudan virus. In FY23, NIAID researchers developed a new experimental vaccine for Sudan virus based on the approach used for rVSV-ZEBOV. This new vaccine, called VSV-SUDV, completely protected macaques against a lethal Sudan virus challenge.[1002] The findings suggest that VSV-SUDV could provide rapid protective immunity against Sudan virus, similar to the protection offered by the rVSV-EBOV vaccine for Ebola.

Mammal Borne Viruses

Animals like rats and bats carry viruses that can spread to people and cause illness, such as Nipah virus and Marburg virus. Fruit bats are the natural host for Nipah virus, and bats are likely also the host for Marburg virus. Neither virus has a vaccine or specific therapy to target it. Nipah virus can cause mild-to-severe disease rapidly progressing from respiratory infection to encephalitis (brain swelling) leading to coma or death. An estimated 40 to 75 percent of people infected with Nipah virus die. Although most cases are transmitted via animals, person-to-person transmission can occur. In FY22, NIAID launched an early-stage, Phase 1 clinical trial evaluating an investigational vaccine to prevent infection with Nipah virus.[1003] Developed by NIAID in collaboration with a pharmaceutical company using mRNA technology, the vaccine was found to be safe, tolerable, and capable of eliciting an immune response in healthy adults.

Marburg virus is in the same virus family as Ebola virus and it causes a similar disease as Ebola. In FY23, results from a 2018-2019 first-in-human Phase 1 clinical trial were published demonstrating that an experimental Marburg virus vaccine, cAd3-Marburg, was safe and induced a strong immune response in

[1000] PREVAC Study Team; et al. N Engl J Med. 2022 Dec 29;387(26):2411-2424. Epub 2022 Dec 14. PMID: 36516078.
[1001] https://www.merck.com/news/u-s-fda-approves-mercks-ervebo-ebola-zaire-vaccine-live-for-use-in-children-12-months-of-age-and-older/
[1002] Marzi A, et al. Lancet Microbe. 2023 Mar;4(3):e171-e178. Epub 2023 Feb 2. PMID: 36739878.
[1003] https://www.niaid.nih.gov/news-events/nih-launches-clinical-trial-mrna-nipah-virus-vaccine

healthy adults.[1004] The vaccine was well-tolerated with no serious adverse events, and 95 percent of participants showed a robust antibody response, with 70 percent maintaining this response for over 48 weeks.

Unknown Etiology

Scientists are striving to better understand acute flaccid myelitis, which is like polio. Symptoms include some paralysis, such as onset of arm or leg weakness and decreased reflexes; and in some cases, difficulty moving the eyes, speaking, swallowing, or breathing. It has emerged in the U.S. over the last decade, with spikes in cases every other year, primarily in the late-summer months. The CDC identified increases in cases in 2014, 2016, and 2018. It can be caused by viruses including enteroviruses, flaviviruses (West Nile virus, Japanese encephalitis virus) and herpesviruses; but scientists still do not know what triggers it in people.[1005] The enterovirus, EV-D68, is a virus of growing public health concern due to its association with severe respiratory and neurological diseases like acute flaccid myelitis. Researchers identified a neutralizing antibody from recovering patients and further developed it for testing.[1006] In FY24, NIAID sponsored a clinical trial to evaluate the safety of the antibody for treating EV-D68.[1007]

Antimicrobial Resistance

Bacteria, fungi, and other microbes evolve over time and can develop resistance to antimicrobial drugs. Microbes naturally develop resistance; however, using antibiotics too often in humans and animals and in cases where antibiotics are not an appropriate treatment can make resistance develop more quickly. Antimicrobial resistance is a significant public health problem in the U.S. and around the world as infections are becoming increasingly difficult to treat, especially in health care facilities and in people with weakened immune systems.

Staphylococcus aureus is a bacteria that often lives in the nose, on the body, and in the gut without causing any harm. However, if the skin barrier is broken, or the immune system compromised, these colonizing bacteria can cause serious skin, bone, lung, and blood infections. Complicating matters further, *S. aureus* is also known to evolve in response to antibiotic treatment and gain resistance. In FY23, a Phase 2 clinical trial demonstrated the effectiveness of using the probiotic *Bacillus subtilis* to reduce *S. aureus* colonization in the body, offering a promising alternative to antibiotics.[1008] This approach potentially preserves the gut microbiota and minimizes antibiotic resistance risk. The study suggests a need to explore intestinal *S. aureus* colonization as a target, revisiting conventional staph infection prevention methods.

[1004] Hamer MJ, et al. Lancet. 2023 Jan 28;401(10373):294-302. PMID: 36709074.
[1005] https://www.cdc.gov/acute-flaccid-myelitis/about/index.html
[1006] Vogt MR, et al. Sci Immunol. 2020 Jul 3;5(49):eaba4902. Erratum in: Sci Immunol. 2020 Sep 18;5(51):eabe5512. PMID: 32620559.
[1007] https://www.niaid.nih.gov/news-events/nih-sponsored-trial-enterovirus-d68-therapeutic-begins
[1008] Piewngam P, et al. Lancet Microbe. 2023 Feb;4(2):e75-e83. Epub 2023 Jan 13. PMID: 36646104.

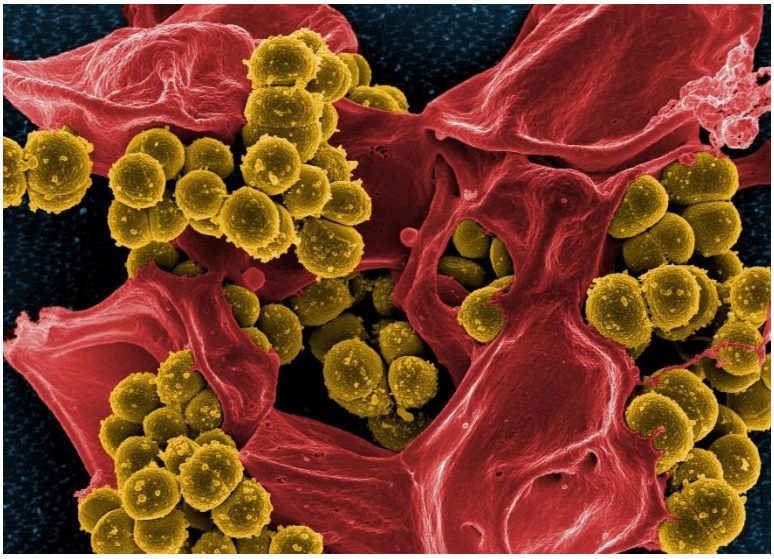


Figure 43. Scanning electron micrograph of methicillin-resistant Staphylococcus aureus bacteria (yellow) and a dead human white blood cell (red). Credit: NIAID/NIH

Treatment of lung disease due to *Mycobacterium abscessus* requires multiple antibiotics. Due to intrinsic and acquired antimicrobial resistance in *M. abscessus* and poor clinical outcomes, it is critical to understand the development of antibiotic resistance both within the host and in the setting of outbreaks. In a podcast episode, trainees from an NIH-funded training program on antimicrobial resistance discussed 2024's most relevant research in the field, and one of the papers highlighted unveiled the mechanism by which *M. abscessus* acquired resistance to a type of antibiotic, Imipenem, in a cystic fibrosis center outbreak.[1009,1010] The findings support using a cocktail of two different drugs for treating *M. abscessus*.

NIAID conducts and supports research to address the significant health challenges posted by sexually transmitted infections (STIs), especially those that acquire antimicrobial resistance. For example, one recent study investigated the efficacy of a common, broad-spectrum antibiotic, doxycycline, as a preventive measure against STIs in various populations at higher risk of acquiring HIV.[1011] The post-exposure prophylaxis method called doxy-PEP showed a two-third reduction in the incidence of syphilis, gonorrhea, and chlamydia, when taken within 72 hours after unprotected sex. However, the researchers highlighted a concern over increased antibacterial resistance to doxycycline.[1012] A second study found the doxy-PEP was ineffective in preventing STIs among women, demonstrating that further study is needed.[1013] In an international Phase 3 trial, a single oral dose of the novel antibiotic Zoliflodacin was shown to be as safe and effective as a current treatment for uncomplicated urogenital gonorrhea.[1014] This development is

[1009] https://asm.org/podcasts/editors-in-conversation/episodes/best-papers-of-aac,-2024-eic-93
[1010] Le Run E, et al. Antimicrob Agents Chemother. 2024 Oct 8;68(10):e0067324. Epub 2024 Sep 10. PMID: 39254295.
[1011] Flores J, et al. JAMA. 2025 Jan 21;333(3):248-249. PMID: 39699880.
[1012] Luetkemeyer AF, et al. N Engl J Med. 2023 Apr 6;388(14):1296-1306. PMID: 37018493.
[1013] https://www.niaid.nih.gov/news-events/biomedical-sti-prevention-evidence-inadequate-cisgender-women
[1014] Taylor SN, et al. N Engl J Med. 2018 Nov 8;379(19):1835-1845. PMID: 30403954.

crucial due to growing resistance to existing antibiotics used to treat gonorrhea caused by the bacteria *Neisseria gonorrhoeae*. Zoliflodacin, which represents a new class of antibiotics, might provide an alternative treatment option, addressing the urgent need for more effective therapies against resistant gonorrhea infections.

Finally, in FY23, NIH launched the *NIH Strategic Plan for Herpes Simplex Virus (HSV) Research*, which was developed by an NIH-wide HSV Working Group with input from over 100 stakeholders in the research and advocacy communities.[1015] HSV-1 and HSV-2 are common infections in the U.S., causing recurring sores and severe complications like viral encephalitis and neonatal herpes. There is no cure or vaccine to protect against HSV, and current treatments only manage symptoms. The strategic plan outlines four strategic priorities: enhancing knowledge of HSV biology; improving diagnosis; advancing treatment strategies, including for resistant infections; and preventing infection. This strategic plan aims to provide a framework for researchers and public health entities to collaboratively mitigate the impact of HSV.

Infectious Disease and Countermeasures Infrastructure

Well-funded and organized infrastructure is essential to coordinating the research and clinical care needed 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.

Collaboration and Capacity Building

A consortium of 21 NIH ICs and the OD pooled funds to understand the social, behavioral, and economic health impacts of the COVID-19 pandemic. [1016] These lessons learned will be instrumental in preparing for future public health emergencies involving infectious diseases. The consortium will support studies to: improve prediction of the impact of COVID-19 mitigation efforts on transmission reduction and on social and economic outcomes; assess the downstream health and healthcare access effects of the economic downturn through analysis of a wide range of data sources; and develop digital and community interventions to ameliorate health effects of COVID-19 mitigation strategies in all populations. These studies create unique opportunities for new research collaborations and networking among investigators and the broader research community. The consortium will disseminate research results to the public.

At the start of the COVID-19 pandemic, NIBIB established the NIH Rapid Acceleration of Diagnostics (RADx®) initiative, comprised of multiple programs designed to rapidly increase the COVID-19 testing capacity in the U.S. One of the programs, RADx® Tech, expanded existing NIBIB programs in point-of-care and at-home test technology development to accelerate the development of new tests for COVID-19 and bring them to market, delivering over eight billion tests and test products and over 75 FDA authorizations and clearances. Another RADx® program, the Independent Test Assessment Program, worked to accelerate regulatory review and availability of high-quality, accurate, and reliable over-the-counter

[1015] https://www.niaid.nih.gov/news-events/nih-releases-strategic-plan-research-herpes-simplex-virus-1-and-2
[1016] https://www.nia.nih.gov/research/dbsr/social-behavioral-and-economic-sbe-research-covid-19-vulnerable-and-health-disparity

COVID-19 tests to the public.[1017] Since FY22, it guided over 40 products through FDA authorization or clearance, including multiplexed tests for influenza and COVID-19, either designed for use at point-of-care settings or in one's own home. NIBIB also applied the strategies learned from the RADx® Tech program to address a range of other health problems, bringing new products to market on greatly accelerated timelines. RADx® efforts include developing technologies to address the maternal health crisis in the U.S., emergency diagnostics for viruses, diagnostics to support the elimination of hepatitis C in the U.S., and much more.

In FY23, NIBIB, in collaboration with the Administration for Strategic Preparedness and Response and CDC, launched a unique, entirely virtual community health intervention program. The nationwide Home Test to Treat program provided at-home rapid COVID-19 and flu tests, telehealth sessions, and lifesaving treatments to underserved populations.[1018] As part of the program, participants received free tests and treatments without ever leaving home. The program enrolled more than 80,000 individuals who received free telehealth services; more than 8,500 program participants tested positive and received free telehealth services; and 7,000+ antiviral prescriptions were given based on the telehealth visits. This program, along with the RADx® program, provide frameworks for quickly responding to future infectious disease threats; in addition to templates to quickly advance diagnostics and treatments for a wide variety of diseases, including chronic diseases.

Pandemic Preparedness

In FY22, NIAID released its new Pandemic Preparedness Plan, which focuses its preparedness efforts on two fronts.[1019] The first involves identifying 'prototype pathogens' within viral families that could significantly impact human health, enabling rapid response by leveraging past research on similar viruses. The second focuses on 'priority pathogens'—viruses known to pose serious risks to human health. NIAID aims to support foundational and preclinical research to better understand prototype and priority pathogens to facilitate development of diagnostics, therapeutics, and vaccines. The plan also highlights comprehensive efforts in epidemiology and pathogen discovery, infrastructure enhancements, and technological advancements, in collaboration with domestic and international partners.

In FY22, NIAID awarded over $12 million to enhance antiviral therapies targeting viruses with pandemic potential as part of the Antiviral Program for Pandemics.[1020] This initiative aims to streamline the discovery, development, and production of antiviral medications. The key focus is on creating drugs that act directly against viruses. The program is also dedicated to finding and developing antivirals for seven viral families with pandemic potential. The program seeks to establish a collection of antivirals that are ready for Phase 2/3 clinical trials for future outbreaks; the flagship program are the nine, newly founded Antiviral Drug Discovery Centers.[1021] In FY24, NIH, led by NIAID, established the Research and Development of Vaccines

[1017] https://www.nibib.nih.gov/programs/radx-innovation-funnel
[1018] https://www.nibib.nih.gov/news-events/newsroom/home-test-treat-program-extends-nationwide
[1019] https://www.niaid.nih.gov/news-events/niaid-pandemic-preparedness-plan-targets-prototype-and-priority-pathogens
[1020] https://www.niaid.nih.gov/news-events/nih-awards-12-million-antiviral-therapeutic-development
[1021] https://www.niaid.nih.gov/research/antiviral-drug-discovery-centers-pathogens-pandemic-concern

and Monoclonal Antibodies for Pandemic Preparedness network.[1022] The network will conduct basic and translational research to develop generalizable vaccine and monoclonal antibody strategies using 'prototype pathogens' within nine virus families—many of which have caused human disease for millennia, have a high likelihood of becoming pandemic threats in the future, or have no existing medical countermeasures.[1023]

NIAID also established the Pandemic Response Repository through Microbial and Immune Surveillance and Epidemiology program to identify, develop, and translate immune-based solutions for circulating and emerging pathogens. The program pairs virologic and immunologic surveillance of viruses and facilitates the development of diagnostic tests and medical countermeasures in anticipation of potential pandemic threats. For example, the program successfully enrolled all cohorts for an observational study to profile gaps in immunity for the enterovirus EV-D68 and other respiratory viruses in children 10 and younger.[1024,1025,1026]

Public Health Emergency Preparedness

Public health emergencies arise when unexpected incidents, both natural and human-made, have the potential to significantly influence the health of a population, necessitating a rapid and robust response. HHS is a national leader in responding to such incidents, and many agencies within HHS, including NIH, 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 decades of research. Multiple NIH ICOs 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 human-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 many current efforts are highlighted below, and additional efforts to understand and respond to infectious diseases are highlighted in the Infectious Diseases and Countermeasures section above.

Emergency Preparedness Across NIH

To ensure NIH is able to respond to public health emergencies quickly, OBSSR, in collaboration with several NIH ICOs, established an accelerated review and award process to fund research addressing emergent and unpredictable health events, such as environmental threats, pandemics, or natural disasters.[1027] By rapidly

[1022] https://www.nih.gov/news-events/news-releases/nih-awards-establish-pandemic-preparedness-research-network
[1023] https://www.niaid.nih.gov/research/vaccines-and-monoclonal-antibodies-pandemic-preparedness-revampp
[1024] Nguyen-Tran H, et al. Lancet Microbe. 2022 Feb;3(2):e83-e85. Epub 2022 Jan 7. PMID: 35036969.
[1025] Park SW, et al. Epidemics. 2024 Mar;46:100736. Epub 2023 Dec 18. PMID: 38118274.
[1026] Nguyen-Tran H, et al. Contemp Clin Trials Commun. 2024 Aug 14;41:101351. PMID: 39252862.
[1027] https://grants.nih.gov/grants/guide/pa-files/PAR-22-233.html

mobilizing research around time-sensitive issues, the program ensures timely generation of critical health data to inform immediate and future responses.

NIEHS played a leading role in the February 2023 East Palestine train derailment response, helping to strengthen localized disaster response capacity. Following the release of hazardous pollutants, NIEHS mobilized research teams to collect environmental and health data from affected residents in East Palestine, Ohio. These populations—primarily middle-class workers and small farmers—faced acute and potentially long-term exposures.[1028] In November 2023, NIEHS and the National Academies convened a workshop to establish public health research and surveillance priorities in the region.

To better understand long-term health risks of environmental pollutants, NIEHS has also led efforts to investigate the biological effects of microplastics and the much smaller nanoplastics. NIEHS invited research proposals examining how these plastic particles, often contaminated with chemicals, pathogens, or metals, may affect human health. [1029] The initiative aims to clarify routes of exposure—through air, water, soil, or food—and the biological pathways these pollutants may disrupt, to identify strategies for better proactive public health interventions.

NIEHS and NIDA co-funded the multiphasic Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription Program[1030]. This program examines how toxicant exposure can drive disease through epigenetic changes—alterations in gene expression that do not modify DNA sequences. For example, exposure to heavy metals like arsenic and nickel are associated with epigenetic changes linked to cancer, autoimmune conditions, and neurological disorders. Insights gained from this program will be essential for helping to identify biomarkers and therapeutic targets in populations exposed to hazardous substances.[1031,1032]

Efforts to translate environmental health science into community-level action are also underway. The NIEHS Collaborative Centers in Children's Environmental Health Research and Translation[1033] program has established a national network of seven centers to apply research findings toward improving children's health. Six centers focus on developing tools and interventions to improve children's health in communities with disproportionate exposure to environmental hazards. A coordinating center promotes collaboration and evaluates network-wide impact. By prioritizing knowledge translation to communities, the program exemplifies how science can be transformed into meaningful health outcomes for all populations.

Air pollution is associated with many health problems like decreased lung function, increased hospital visits, worsening asthma symptoms, and increases in premature deaths. NIEHS has advanced our understanding of how air pollution contributes to chronic disease risks beginning in childhood. A study examining traffic-related air pollution found associations with biomarkers for blood sugar dysregulation,

[1028] Oladeji, O., et al. Environ Sci Technol Lett. 2023 Jul 12;10(8):680-685. PMID: 37577363.
[1029] https://grants.nih.gov/grants/guide/notice-files/NOT-ES-23-002.html
[1030] https://www.niehs.nih.gov/research/supported/health/envepi/target
[1031] Viet, S. M., et al. Int J Hyg Environ Health. 2021 Jun;235:113768. PMID: 34034040.
[1032] Wang T, et al. Nat Biotechnol. 2018 Mar 6;36(3):225-227. PMID: 29509741.
[1033] https://www.niehs.nih.gov/research/supported/centers/collaborative

elevated blood pressure, and oxidative stress in children—early indicators of metabolic syndrome. These findings suggest that childhood exposure to polluted air may set the stage for lifelong cardiovascular risks.[1034]

Complementing these insights, a study led by NIMHD, in collaboration with NIEHS, revealed that prenatal exposure to ambient air pollution negatively impacts neurodevelopmental outcomes in early childhood. Infants born to mothers with higher pollutant exposure during mid- and late-pregnancy scored lower on motor, cognitive, and language assessments at age two. This research highlights the importance of protecting maternal health and reducing environmental exposure during critical developmental windows.[1035]

NIH also supports research to protect against, and respond to, chemical and radiological disasters.[1036] For example, the Chemical Countermeasures Research Program, led by NIAID with support from six other NIH ICs, develops medical countermeasures to mitigate the effects of toxic chemical exposure.[1037] NIDA-supported research, which is focused on countermeasures to the toxicity associated with potent opioids, led to the discovery that toxicity due to opioids may be prevented by a peripheral acting antagonist, without precipitating opioid withdrawal.[1038] By exploring antidotes and early-stage therapeutics, the program strengthens national preparedness against high-consequence chemical threats.

To improve responses to radiological disasters, NIAID launched a first-in-human clinical trial evaluating HOPO 14-1,[1039] an experimental oral drug designed to remove radioactive contamination from the body. The Phase 1 trial is focused on establishing the safety and tolerability of the oral capsule in healthy volunteers. Unlike current intravenous treatments, HOPO 14-1's oral formulation offers a significant logistical advantage for emergency stockpiling and deployment. With encouraging preclinical results showing high efficacy in removing uranium and neptunium, this development could revolutionize public health response to radiological threats.

Ferroptosis is a cell death process associated with pathogenesis in brain trauma, Alzheimer's Disease, and acute radiation syndrome. Unlike apoptosis, the more common and better understood process of cell death, ferroptosis is not a routine part of a cell's life cycle, and scientists have struggled with methods to control it. NCATS-supported scientists have developed and tested two new ferroptosis inhibitors, FerroLOXIN-1 and FerroLOXIN-2, which block the enzyme 15LOX-2 when it combines with the protein PEBP1 at the start of ferroptosis.[1040] Test results showed that both inhibitors prevented ferroptosis in human lung cells and increased survival in mice with acute radiation syndrome, highlighting their potential as a new class of targeted therapies and paving the way for further studies.[1041]

[1034] Mann, et. al. Environ Res. 2021 Apr;195:110870. PMID: 33587949.
[1035] Morgan ZEM, et al. Environ Health. 2023 Jan 24;22(1):11. PMID: 36694159.
[1036] https://www.niaid.nih.gov/research/biodefense
[1037] https://www.niaid.nih.gov/research/chemical-countermeasures-program
[1038] Ruyle, B. C., et al. (2025). eLife, 13, RP104469, 40167443.
[1039] https://www.niaid.nih.gov/news-events/first-human-trial-oral-drug-remove-radioactive-contamination-begins
[1040] https://ncats.nih.gov/news-events/news/scientists-build-ferroptosis-inhibitors-to-curb-cell-death-process-linked-to-alzheimers-disease-and-cancer
[1041] Dar HH, et al. Proc Natl Acad Sci U S A. 2023 Jun 20;120(25):e2218896120. Epub 2023 Jun 16. PMID: 37327313.

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.[1042] Although such diseases are individually rare, collectively, an estimated 25 to 30 million Americans are affected—that is about one in ten people.[1043] 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 estimated 10,000 rare and neglected diseases, only about 500 have approved treatments.[1044]

Summary of NIH Activities

NIH funding for rare diseases was $6.5 billion in FY22, $6.9 billion in FY23, and $6.8 billion in FY24.[1045] Since rare and undiagnosed diseases can impact any organ system, funded research and activities are supported by many NIH ICOs, 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.

Understanding Rare and 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.

For example, the NIH Undiagnosed Diseases Network (UDN) aims to improve the diagnosis of rare and undiagnosed conditions. Leveraging advances in medical and genomic research, the UDN has established exemplary clinical practices, standards, and pipelines for genomics-based diagnoses that can inform patient care.[1046] Since its launch by the NIH Common Fund in 2013, the UDN has made over 800 diagnoses including new diseases and syndromes and identified new disease-linked genes and genomic variants. NINDS has played a major part in the UDN, given that many cases have neurologic involvement, and in FY23, the UDN transitioned to NINDS leadership with NIH-wide collaboration to sustain and expand the program to reach a greater number and breadth of participants.

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 also unique challenges in optimizing study design, patient

[1042] https://www.congress.gov/107/plaws/publ280/PLAW-107publ280.pdf
[1043] https://www.nih.gov/about-nih/nih-turning-discovery-into-health/promise-precision-medicine/rare-diseases
[1044] https://rarediseases.info.nih.gov/
[1045] https://report.nih.gov/funding/categorical-spending#/
[1046] https://www.ninds.nih.gov/current-research/focus-disorders/focus-undiagnosed-diseases-network

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 at the end 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 Clinical Center co-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.[1047]



Figure 44. Panelists at Rare Disease Day at NIH. Credit: Daniel Soñé Photography

Evolving from NIH's participation in the International Human Genome Sequencing Project, the NHGRI Genome Sequencing Program works to discover the genomic bases of rare and common diseases.[1048] The Program identifies genomic variants that either increase or decrease risk associated with common diseases and aims to discover the genomic bases for rare Mendelian diseases (diseases caused by a mutation in a single gene). It also supports development of methods, tools, and knowledge available to the biomedical research community.

The Genomics Research Elucidates Genetics of Rare Diseases Consortium aims to increase the proportion of Mendelian disorders 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.[1049] In its first three years, the consortium generated a robust dataset containing a variety of data types collected from over 1,000 families. This dataset is readily available to the research community

[1047] https://ncats.nih.gov/news-events/events/rdd
[1048] https://www.genome.gov/Funded-Programs-Projects/NHGRI-Genome-Sequencing-Program
[1049] https://www.genome.gov/Funded-Programs-Projects/GREGOR-Consortium

through the NHGRI Genomic Data Science Analysis, Visualization and Informatics Lab-space.[1050] Publications citing consortium grants have been cited by over 2,300 papers.[1051]

Led by NIH, the Human Genome Project revealed that humans have slightly less than 20,000 protein-coding genes, yet more than 75 percent of protein research continues to focus on approximately 10 percent, or around 200, of those protein-coded genes. The Common Fund's Illuminating the Druggabale Genome Program[1052] aims to improve our understanding of these understudied proteins; and awarded a small pilot grant, in partnership with NCATS, to study the role of RIght Open reading frame Kinase 3. At the time of award, this protein was considered to be significantly understudied, with only eight publications, eight possible protein interaction partners, and one small molecule ligand identified.[1053] The findings from this study led to a partnership with a small business and a subsequent small business award to design small molecules to block this protein to treat cutaneous lupus erythematosus, a rare skin autoimmune disease. There are now 21 publications, 145 possible protein interaction partners, and two small-molecule ligands. This work highlights two important themes: that small pilot projects can achieve significant scientific outputs and greater research of understudied proteins could help treat many common and rare diseases.

Interventions and Treatments

Severe combined immunodeficiency (SCID) is a rare genetic disease that comes in different forms, each caused by mutations in genes for the development of infection-fighting immune cells. Without treatment to restore the immune system, children rarely live past two years of age. Funded through the Rare Diseases Clinical Research Network and NIAID, scientists examined data on more than 900 children with SCID and found that widespread newborn screening for SCID, followed by early treatment, boosted the five-year survival rate of children with the disorder from 73 percent before screening began to 87 percent.[1054] Children whose SCID was suspected based on newborn screening had higher five-year survival rates after treatment than those suspected based on getting sick or family history. This research highlights the effectiveness of early detection in preventing life-threatening infections in infants with SCID.

The NCATS-lead Bespoke Gene Therapy Consortium, part of the AMP Program, is establishing platforms and standards to speed the development and delivery of customized gene therapies that could treat millions of people affected by rare diseases. In May 2023, the consortium announced the selection of eight rare diseases for its clinical trial portfolio.[1055,1056] Moreover, FDA granted NCATS both Rare Pediatric Disease and Orphan Drug Designations for five investigational gene therapies, which are key to the consortium's mission to streamline the development of bespoke gene therapies for extremely rare diseases of no

[1050] https://www.genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/Genomic-Analysis-Visualization-Informatics-Lab-space-AnVIL
[1051] https://gregorconsortium.org/publications/view
[1052] https://commonfund.nih.gov/idg
[1053] Bisom TC, et al. Viruses. 2023 Jul 18;15(7):1566. PMID: 37515252.
[1054] Thakar MS, et al. Lancet. 2023 Jul 8;402(10396):129-140. PMID: 37352885.
[1055] https://ncats.nih.gov/news-events/news/new-fda-designations-may-jumpstart-gene-therapy-development
[1056] https://ncats.nih.gov/research/research-activities/gene-targeted-therapies/bgtc-bespoke-gene-therapy-consortium

commercial interest. To assist others in this process, in February 2024, the consortium published their Regulatory Playbook, covering critical aspects of development up to Investigational New Drug FDA submission and first-in-human studies.[1057,1058] This playbook is intended to act as a roadmap for streamlining product development and navigation of the regulatory pathway, with the goal of getting new treatments to patients sooner.

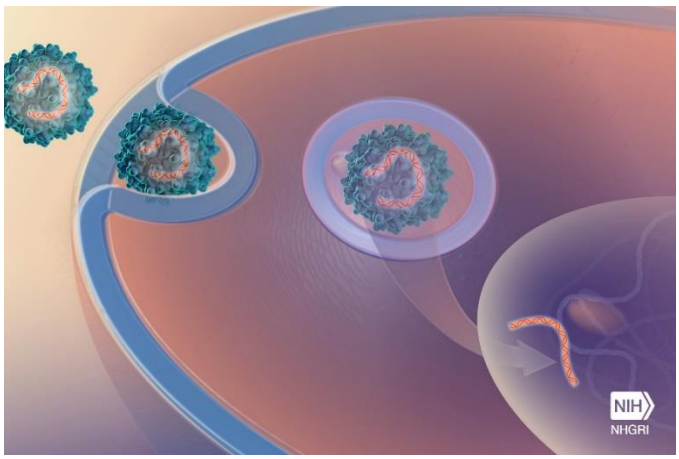


Figure 45. Gene therapy involves the insertion of a functional copy of a gene into cells with a defective copy of that gene. Providing a functional copy compensates for the defective copy and cures the disease that was caused by the defective gene. Credit: Darryl Leja, NHGRI/NIH

The Platform Vector Gene Therapy program is a joint initiative involving NICHD, NCATS, NINDS, and NHGRI that is examining the use of a standardized gene therapy delivery approach and manufacturing system to accelerate rare disease clinical trials.[1059] By standardizing experimental approaches, researchers can look at how identical gene therapy vectors differ in efficacy depending on the disease being treated. From this, they can create a plug-and-play roadmap to advance targeted cures for other rare diseases. Examples of recent achievements include NCATS receiving the Orphan Drug Designation for an investigational gene therapy to treat a form of propionic acidemia, a rare metabolic disorder.[1060,1061] NCATS also received a Rare Pediatric Disease designation for propionic acidemia—a rare inherited metabolic disorder—and provided templates of the model for others who are developing gene therapies.[1062]

The NINDS Ultra-rare Gene-based Therapy Network supports precision medicine therapy development for ultra-rare neurological diseases affecting as few or fewer than one in 50,000 people.[1063] Combined, these often serious and life-threatening diseases represent a large medical need without available treatments.

[1057] https://bgtcplaybook.document360.io/
[1058] Brooks PJ, et al. Nat Rev Drug Discov. 2024 Mar;23(3):157-158. PMID: 38321319.
[1059] https://ncats.nih.gov/research/research-activities/gene-targeted-therapies/pave-gt-platform-vector-gene-therapy
[1060] Lomash RM, et al. Hum Gene Ther. 2023 Mar;34(5-6):217-227. PMID: 36694456.
[1061] https://pave-gt.ncats.nih.gov/news/ncats-receives-fda-orphan-drug-designation-to-treat-propionic-acidemia/
[1062] https://ncats.nih.gov/news-events/news/2023/NIH-Gene-Therapy-Team-Reveals-Its-Path-to-FDA-Orphan-Drug-and-Rare-Pediatric-Disease-Designations
[1063] https://www.ninds.nih.gov/current-research/research-funded-ninds/translational-research/ultra-rare-gene-based-therapy-urgent-network

Since most are single-gene disorders, they are excellent candidates for gene-based therapy. This network provides funding and resources to advance gene-based therapies for ultra-rare neurological diseases from late-stage pre-clinical development into first-in-human clinical testing. The program launched its first five projects in FY23 and FY24.

Sorbitol dehydrogenase deficiency is caused by a mutation in the *SORD* gene and leads to hereditary neuropathy, a set of clinically and genetically distinct conditions affecting the peripheral nerves. Investigators supported by the Rare Diseases Clinical Research Network demonstrated that mutations in the sorbitol dehydrogenase gene are responsible for disease in a subset of patients, and lead to a loss of the enzymatic function and consequent accumulation of sorbitol (a sugar alcohol molecule) in cells.[1064] A pilot study in patients with this deficiency showed that sorbitol levels correlated with disease severity, and treatment with govorestat, an inhibitor of the protein that generates sorbitol, substantially reduced sorbitol levels. These proof-of-concept results provided the impetus for a registrational Phase 3 study of govorestat. These findings are an example of rare diseases informing common health issues, as the identification of sorbitol dehydrogenase-associated neuropathy may have broader implications for the fields of diabetic neuropathy (nerve damage) and retinopathy (damage to the retina in the eye).

Alveolar soft part sarcoma is an extremely rare cancer that develops in different types of soft tissues, such as muscle, fat, or nerves. It has proven difficult to treat and affects mostly adolescents and young adults. In 2023, results from an NCI-led clinical trial led to FDA approval of the immunotherapy drug atezolizumab for the treatment of this cancer. [1065,1066] Importantly, this is the first approved treatment for advanced alveolar soft part sarcoma, and the first time that this drug has been approved for children, providing an important therapeutic option for this a rare disease that has been challenging to treat.

Researchers at NCI and NIAID found that immunotherapy substantially increases survival of people with lymphomatoid granulomatosis—a rare precancerous condition driven by the Epstein-Barr virus that can progress to a high-grade form if left untreated and subsequently to an aggressive and fatal B-cell lymphoma. Patients who received this immunotherapy treatment lived for a median of 20 years, compared to less than 2 years for people who had developed high-grade disease prior to treatment development, showing a significant improvement in survival outcomes that can inform a new standard of care for this rare disease. [1067,1068] This study took 30 years to complete and highlights the unique ability of the NIH intramural program to conduct long-term studies that may not be possible in other research settings, such as longitudinal studies or clinical trials that may take decades to complete due to disease rarity and the associated challenge of recruiting patients to participate.

In the rare disease fibrodysplasia ossificans progressiva, bone forms in places that it does not belong, such as muscle and other connective tissues, thereby limiting a person's ability to move. Research supported

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[1064] Zhu Y, et al. JCI Insight. 2023 May 22;8(10):e164954. PMID: 37014713.
[1065] https://www.cancer.gov/news-events/press-releases/2022/nci-trial-atezolizumab-approval-alveolar-soft-part-sarcoma
[1066] Chen AP, et al. N Engl J Med. 2023 Sep 7;389(10):911-921. PMID: 37672694.
[1067] https://www.nih.gov/news-events/news-releases/nih-study-finds-immunotherapy-substantially-increases-survival-people-lymphomatoid-granulomatosis
[1068] Melani C, et al. Lancet Haematol. 2023 May;10(5):e346-e358. PMID: 37011643.

by NIAMS has uncovered fundamental biological processes underlying this disease and provided the foundation for developing the first FDA-approved treatment.[1069,1070,1071]

Another rare bone disease, fibrous dysplasia, causes lesions in the bone, which are marked by accelerated bone turnover and weakened bones, leading to bone deformities, fractures, physical disabilities, and pain. In some cases, the lesions can press up against organs and nerves, impairing functions like vision and breathing. In a Phase 2 clinical trial, NIDCR intramural researchers examined the effects and safety of denosumab, a medication licensed by FDA to treat bone problems from osteoporosis and cancer, to treat fibrous dysplasia.[1072] At the end of the treatment period, results indicated that the treatment improved the quality and strength of patients' bones as well as reduced related complications, including better lung function and vision improvement.

Calcium is important for the proper functioning of many organs and tissues, including bones, teeth, heart, muscles, and nerves. For people with the rare genetic disorder called autosomal dominant hypocalcemia type 1, calcium levels in the blood are unusually low, leading to symptoms that can range from tingling limbs, muscle cramps, and brain fog to life-threatening seizures. While current therapies can help manage symptoms, there are no approved treatments that address the root cause of the condition. NIDCR intramural researchers found that an investigational drug, encaleret, restored calcium levels in patients with autosomal dominant hypocalcemia type 1.[1073] An additional study will determine if this treatment can also be used to help correct calcium levels in people whose parathyroid glands, which regulate blood calcium levels, have been damaged by surgery.

NIH researchers found a new treatment for autoimmune polyendocrine syndrome type 1, a rare genetic disorder that causes multi-organ dysfunction, usually beginning in childhood, and can kill up to 30 percent of people with the syndrome. NIAID-led scientists' discovery of a hidden gene variant that causes some cases of this devastating inherited disease will enable earlier diagnosis of the disorder in people with the variant, facilitating earlier medical care that may prolong their lives.[1074] Researchers found that this syndrome was associated with elevated levels of interferon-gamma (a protein involved in fighting off infections and cancers), and that the FDA-approved drug ruxolitinib was able to reduce interferon-gamma activity in mice and humans, leading to improved symptoms in affected individuals.[1075] A Phase 2 trial of the drug is underway.[1076]

Hereditary Hemorrhagic Telangiectasia (HHT) is a rare genetic disorder that affects 1 in 5,000 people worldwide. This disorder leads to malformed blood vessels that cause excessive bleeding from the nose and gastrointestinal tract, requiring medical treatment and blood transfusions and impairing patients'

[1069] Aykul S, et al. J Clin Invest. 2022 Jun 15;132(12):e153792. PMID: 35511419.
[1070] Lees-Shepard JB, et al. J Clin Invest. 2022 Jun 15;132(12):e153795. PMID: 35503416.
[1071] Yamamoto M, et al. J Bone Miner Res. 2022 Nov;37(11):2077-2093. PMID: 35637634.
[1072] de Castro LF, et al. N Engl J Med. 2023 Feb 23;388(8):766-768. PMID: 36812441.
[1073] Gafni RI, et al. N Engl J Med. 2023 Sep 28;389(13):1245-1247. PMID: 37754292.
[1074] https://www.niaid.nih.gov/news-events/scientists-discover-cause-potential-treatment-deadly-autoimmune-disorder
[1075] Oikonomou V, et al. N Engl J Med. 2024 May 30;390(20):1873-1884. PMID: 38810185.
[1076] https://www.niaid.nih.gov/clinical-trials/efficacy-and-safety-ruxolitinib-hair-regrowth-patients-apeced-associated-alopecia

quality of life. Historically, there have been no effective medical therapies for HHT. With the active support of the patient organization called Cure HHT, a recent NHLBI-supported clinical trial achieved sufficient patient enrollment and ended earlier than expected, with positive results. The study found that pomalidomide, an oral medication approved by FDA to treat some cancers, was effective in treating bleeding in hereditary hemorrhagic telangiectasia.[1077]

Health Disparities

Diseases do not affect individuals and groups equally. They vary substantially across sociodemographic characteristics, including geography, socioeconomic status, and race and/or ethnicity. As the Nation's steward of biomedical research, NIH has devoted considerable resources to studying health disparities in order to ensure that all Americans have the opportunity to live a longer, healthier, and happier life. Health disparities research science focuses on modifiable health differences that exist between specific population groups. Health disparities may be observed in the risks, prevalence, or problems resulting from specific behaviors, as well as the incidence, prevalence, and mortality from conditions, diseases, and/or disorders. Health disparities also can be observed in health care access, quality, and utilization, and within the delivery of clinical care. By funding and conducting health disparities science, NIH seeks to develop evidence-based interventions to improve the health of all Americans.

Summary of NIH Activities

In accordance with congressional mandates articulated in the *PHS Act*, NIH supports research, research training, and other activities focused on health disparities. Research efforts are multifaceted, including research to prevent, diagnose, and treat a range of diseases and conditions among affected populations. Examples of key focus areas include: identifying patterns and causes of health disparities, building research partnerships with communities, multidisciplinary collaborations, chronic disease research, rural health research, Tribal health research, and prevention research. NIH funding for health disparities research science was $5.2 billion in FY23 and $5.4 billion FY24.[1078]

Health Disparities and their Causes

High-quality data and in-depth analysis are critical for identifying the patterns and causes of health disparities. NIMHD leads a collaborative effort to examine disparities in health outcomes by geography, socioeconomic status, and race and/or ethnicity. The research project uses a proprietary modeling algorithm to integrate data across multiple national data sources to generate county-specific, age-adjusted mortality. This project has generated important scientific findings on health disparities published in high-impact peer-reviewed journals. For example, NIMHD published the first nationwide analysis that highlighted cause-specific mortality in 3,110 U.S. counties over a 20-year period.[1079] The study estimated the geographical variations of causes of mortality across the country and for five racial and/or ethnic groups. It also described the connection between where people live and racial and/or ethnic disparities in mortality, comparing patterns across health conditions. Mortality was higher in the Appalachian areas and

[1077] Al-Samkari H, et al. N Engl J Med. 2024 Sep 19;391(11):1015-1027. PMID: 39292928.
[1078] https://report.nih.gov/funding/categorical-spending#/
[1079] GBD US Health Disparities Collaborators. Lancet 2023;402(10407):1065-1082. PMID: 37544309.

Southern region, as well as certain areas in the Northern Plains. Additionally, mortality was higher for the AI/AN and Black or African American populations than for the other populations, and lowest for Asian Americans, with significant geographic variation within each population.

NIMHD also published the first nationwide analysis of life expectancy using national data at the county level from 2000 to 2019.[1080] Overall life expectancy improved throughout most of the period but flattened and even decreased in the last few years. Geographically, however, only 57% of the U.S. counties experienced significant increases in life expectancies. Analyses by race and/or ethnicity found lower life expectancy among Black or African American, and AI/AN populations, while also observing higher life expectancy among Asian American and Hispanic or Latino populations. NIMHD leveraged this project to further examine disparities in mortality caused by cirrhosis, stomach cancer, liver cancer, and falls.[1081,1082,1083,1084] Harnessing data and trend analyses at the local county level provided evidence for further research to study and increase understanding of the causes of these geography- and demographic-related disparities. These findings also help direct public health and clinical interventions to address these disparities. The public can explore health trends using these county-level life expectancy and cause-specific mortality data via an interactive online map.[1085]

Collecting and analyzing health outcomes across different demographic groups is also foundational to designing effective interventions for at-risk populations. For example, the historic notion that gout is a disease affecting mainly affluent White men who indulge in meaty food and alcohol may have changed over time. NIAMS-funded researchers found that Black men and women were at the highest risk of gout.[1086] Poverty, higher body mass index, and higher prevalence of chronic kidney disease were identified as risk factors in these populations, suggesting that key social and lifestyle factors significantly impact the current racial and sex-specific disparities in gout. This finding has implications for identifying people who may be considered at risk for gout because they may benefit from blood tests that can predict their risk of gout flares and hospitalization for recurrent gout.

Research Partnerships with Communities

Community-engaged research brings people in local communities into the research process, especially people who will benefit from or be impacted by the research. The NIH Community Engagement Alliance, co-led by NHLBI and NIMHD, is a research network that seeks to promote health, improve health outcomes, reduce health disparities, and strengthen community partnerships through community-engaged research.[1087] Supported programs conduct community-engaged research in various areas of public health where communities are disproportionately affected by specific diseases and conditions, such

[1080] GBD US Health Disparities Collaborators. Lancet 2022;400(10345):25-38. PMID: 35717994.
[1081] GBD US Health Disparities Collaborators. Lancet Public Health. 2024 Aug;9(8):e551-e563. Epub 2024 Jul 14. PMID: 39004094.
[1082] GBD US Health Disparities Collaborators. Lancet Reg Health Am. 2023 Aug 4;24:100547. PMID: 37600165.
[1083] GBD US Health Disparities Collaborators. Lancet Public Health. 2024 Mar;9(3):e186-e198. PMID: 38429018.
[1084] GBD US Health Disparities Collaborators. Lancet Public Health. 2024 Aug;9(8):e539-e550. PMID: 39095132.
[1085] https://www.healthdata.org/data-tools-practices/interactive-visuals/us-health-map
[1086] McCormick N, et al. JAMA Netw Open 2022;5(8):e2226804. PMID: 35969396.
[1087] https://ceal.nih.gov/

as chronic diseases, poor nutrition, and lack of access to health care.[1088] The programs partner with communities to build trust in science and research, ensure participation across the research continuum, and advance community-driven solutions to address health disparities. Over the last several years, the Alliance has offered valuable lessons about the important role that community-based health models play in addressing public health information gaps, along with the value of developing community-driven interventions that lead to significant and sustainable change.

The Research Centers in Minority Institutions program at NIMHD has continued to expand the Nation's capacity for health sciences research. Institutions are eligible to compete for a program grant if they have less than an average of $50 million in total NIH support over the previous three years. The investments of NIMHD have facilitated scientific infrastructures at 22 colleges and universities, which include 13 Historically Black Colleges and Universities (as of 2024), a coordinating center, and most recently, a clinical research network at two sites conducting innovative research in partnership with local organizations and communities.[1089,1090] The clinical research network is designed to build capacity for community-based clinicians within health care systems to conduct research on topics such as chronic diseases. The program strengthens institutional ability to conduct quality research in basic, behavioral, clinical, and implementation sciences; creates a network of collaborations in the consortium; and builds community partnerships to advance research. For example, program investigators evaluated a tailored physical activity intervention to improve the quality of life among AI/AN cancer survivors.[1091] Participants in the intervention group experienced significantly higher cardiorespiratory fitness, physical improvement, and decreased fatigue compared with those who maintained existing habits. Familial support was also vital in improving participants' health and well-being.

Multidisciplinary Collaborations

Multidisciplinary research stimulates innovation by bringing together a wide variety of expertise and methodologies to tackle complex health challenges, such as improving maternal health. An estimated 1,200 U.S. women die each year from conditions related to or associated with pregnancy or childbirth, with Black or African American women and AI/AN women having three times and two times the maternal mortality rates of White women, respectively. In addition, maternal mortality rates are 80 percent higher in rural areas compared to large metropolitan areas.[1092] According to CDC, more than 80 percent of pregnancy-related deaths are preventable.[1093] To advance the goals of the NIH-wide Implementing a Maternal health and Pregnancy Outcomes Vision for Everyone initiative, NIMHD and its NIH partners announced a new effort in 2024 to support multidisciplinary and innovative intervention research to understand and address maternal morbidity and mortality in the U.S. The new effort will include low socioeconomic status, underserved rural populations, and racial and/or ethnic minority populations, and

[1088] https://nihceal.org/impact
[1089] https://www.nimhd.nih.gov/research/extramural-research/research-centers/research-centers-minority-institutions-program
[1090] https://rcmi-cc.org/
[1091] Bea, JW, et al. Exerc Sport Mov 2023;1(2):e00007. PMID: 37731941.
[1092] https://archive.cdc.gov/#/details?url=https://www.cdc.gov/maternal-mortality/php/data-research/index.html
[1093] https://www.cdc.gov/maternal-mortality/php/data-research/mmrc-2017-2019.html

will focus on understudied healthcare factors.[1094] This line of research is critical for bridging the knowledge gap about healthcare access and quality across the full spectrum of maternal care and will add to the evidence base for improved maternal care and outcomes.

Epigenomics is a field of biomedical science focusing on DNA modifications associated with changes in gene activity, but without alteration of the underlying DNA sequence. Social epigenomics is the study of how social experiences affect gene activity and, in turn, health and disease risk. The NIMHD Social Epigenomics program aims to advance the science of epigenomics focused on health disparities; expand understanding of how social factors impact epigenetic mechanisms that influence health risks and contribute to health disparities; and promote epigenetics research to better diagnose disease risk or resiliency among populations experiencing health disparities.[1095] The program promotes multidisciplinary collaborations that combine the knowledge and scientific expertise of social scientists, public health researchers, and molecular biologists to develop innovative strategies for understanding the mechanisms that may create or contribute to the persistence of health disparities. In 2024, NIMHD published a special collection of articles on social epigenomics.[1096] Comprising an NIMHD editorial and eleven research papers, the special collection highlighted major discoveries and important scientific progress on social determinants of place-based factors that affect health, health disparities, and their impact on biological pathways and health.

Chronic Disease Research

Chronic diseases—such as cardiovascular disease, diabetes, cancer, and Alzheimer's disease—are the leading cause of illness, disability, and death in the U.S. In 2021, NIMHD funded the establishment of 11 regional comprehensive research centers to study the prevention, treatment, and management of co-occurring chronic diseases that disproportionately affect one or more populations within each region.[1097] These Multiple Chronic Disease Research Centers evaluate new or adapted interventions, strategies for implementing evidence-based interventions or practices, and/or existing interventions implemented by service providers within their regions. Examples of funded projects include testing strategies to reduce chronic diseases among Hispanic or Latino children in Southern California and providing effective interventions to manage cardiometabolic diseases—a group of health problems that affect the heart and the body's metabolism—among populations living in the Deep South. With the support of a research coordinating center, the regional centers actively share and disseminate project findings.

Compared with other racial and/or ethnic groups, Native Hawaiian/Pacific Islander (NHPI) populations have disproportionately high rates of diabetes, heart disease, and other chronic conditions.[1098] The NHPI Health Research Office, established within NIMHD by Congress in 2024 to address health disparities in NHPI communities, aims to advance NIH's efforts to support research, training, and community engagement that promotes and improves the health of NHPI communities in the U.S. and its territories.

[1094] https://grants.nih.gov/grants/guide/pa-files/PAR-24-059.html
[1095] https://www.nimhd.nih.gov/social-epigenomics-research
[1096] Gillman, AS et al. JAMA Netw Open 2024;7(7):e2428992. PMID: 39073810.
[1097] https://www.nimhd.nih.gov/news-events/announcement/nimhd-provides-over-200-million-funding-research-chronic-disease
[1098] https://minorityhealth.hhs.gov/native-hawaiian-and-pacific-islander-health

The Office supports rigorous research, career development, and training for researchers focused on NHPI health, and develops partnerships with academic institutions that have a track record of working closely with NHPI communities and NHPI-serving organizations to build research capacity.[1099]

Despite advances in cancer prevention, diagnosis, treatment, and survival, disparities in cancer outcomes persist. Populations living in poverty in the U.S.—particularly those in persistent poverty—face higher rates of both cancer-specific and overall morbidity and mortality. Areas of persistent poverty are at an increased risk of cancer due to multiple factors, including greater carcinogen exposure, lower educational attainment, lack of adequate housing, food insecurity, and the lack of access to care. All these factors result in increased cancer incidence and delayed cancer diagnosis, treatment, and, subsequently, lower rates of survival. In 2023, NCI made five awards as part of the Persistent Poverty Initiative, committing $50 million over the next five years (pending funding availability) to address factors of persistent poverty in the context of cancer.[1100] This initiative established five new Centers for Cancer Control Research in Persistent Poverty Areas to work with low-income communities in implementing and evaluating interventions for cancer control and prevention, follow-up care, and survivorship. The centers will conduct research in areas such as reducing obesity, improving nutrition, increasing physical activity, and helping people quit smoking. In addition, the centers will help train a pipeline of early-career investigators to work with underserved communities in conducting intervention research.

Rural Health Research

Nearly 46 million Americans live in rural communities, and studies have found that they are more likely to die prematurely from heart and lung diseases. NHLBI developed the Risk Underlying Rural Areas Longitudinal Cohort Study to address a critical gap in research data regarding the health of people in rural parts of the southeastern U.S.[1101] Focusing on 10 rural counties in Alabama, Kentucky, Louisiana, and Mississippi, the study aims to recruit 4,600 residents and examine different aspects of their heart, lung, and general health. The research team, led by a group of scientists from 16 universities, deploys high-tech mobile examination units to collect data from study participants, even those who reside in the most remote areas of the country. To maximize the use of the data collected, it will be added to the analytic platform of NHLBI's Trans-Omics for Precision Medicine program to support discovery of genomic and other complex risk factors that influence health disparities wherever they are found.[1102] The study represents a major effort to bridge the rural research gap by focusing on communities not adequately studied before, and its results will help guide future programs to improve the health of these communities.

Yearly eye screening is recommended by the American Diabetes Association, as early diagnosis and treatment decreases the risk of severe vision loss from diabetic eye disease by more than 90 percent. Data shows that only about half of all Americans with diabetes receive this screening, with rates even lower in rural areas.[1103] To address this problem, in 2021, NEI funded the Implementation of Teleophthalmology in

[1099] https://www.nimhd.nih.gov/research/native-hawaiian-pacific-islander-health-research-office
[1100] https://www.cancer.gov/news-events/press-releases/2023/nci-launches-persistent-poverty-initiative
[1101] https://theruralstudy.org/
[1102] https://topmed.nhlbi.nih.gov/
[1103] https://www.nei.nih.gov/sites/default/files/2019-06/diabetes-prevent-vision-loss.pdf

Rural Health Systems Trial to test the application of remote diabetic retinopathy screening across different rural health systems in the U.S.[1104,1105] Diabetic retinopathy is the leading cause of blindness in working-age adults and is caused by high blood sugar damaging blood vessels in the retina, the part of the eye that receives and processes visual images. Through the study, residents in rural areas have access to diabetic eye screenings that promote early detection and timely treatment to prevent blindness. Moreover, the study is expected to shed light on how primary care clinics can better integrate and increase of the use of remote eye screenings to serve rural communities and other communities where similar screening challenges exist.

Tribal Health Research

NIH is committed to building productive research partnerships with Tribal Nations, to support the development of culturally relevant biomedical and health research vital to improving AI/AN health. In 2015 NIH established the Tribal Health Research Office (THRO) to lead efforts to advance AI/AN health by collaborating with Tribal Nations and across NIH ICOs by strategically leading, consulting, coordinating, and co-funding culturally relevant research; strengthening community research capacity; and cultivating a skilled workforce that promotes Tribal health sovereignty. THRO, in collaboration with NIH ICOs, conducts Tribal consultations to gain important guidance from Tribes and Tribal leaders. A Tribal Consultation is a government-to-government dialogue between official representatives of the Federal Government and Indian Tribes to discuss Federal proposals, before the Federal Government makes decisions on those proposals. Adhering to HHS and NIH policy, NIH regularly initiates Tribal Consultations to ensure meaningful and timely engagements with Indian Tribes before taking any actions that will significantly affect Indian Tribes. For example, in 2023, the *All of Us* Research Program released a Tribal consultation report developed in collaboration with Tribal leaders, establishing best practices for integrating AI/AN data into research. The report highlights culturally appropriate data stewardship and demonstrates the program's commitment to respectful engagement. As part of this initiative, *All of Us* paused the sharing of AI/AN participant data, refined its engagement strategies, and committed to restricting recruitment on Tribal lands without explicit permission. These steps ensure that program activities are in alignment with Tribal values and priorities, promoting respectful and ethical research practices.

Likewise, in 2024, the Office of Science Policy within the NIH OD, and THRO co-led an effort to develop, review, and refine culturally appropriate and acceptable options for the return of biospecimens collected from AI/AN populations. Through a Tribal Consultation, the two offices obtained valuable input from Tribal leaders on five proposed options. NIH is moving toward finalizing the policy to ensure research fairness and respect for Tribal customs and research practices.[1106]

Tribal data sovereignty is the right of each Tribal Nation to exercise their sovereign authority and govern the collection, stewardship, management, sharing, transfer, re-use, disposition, and disposal of data collected from and about their Tribal populations; particularly when such data has the potential to impact the economic, social, cultural, and general welfare of their Tribal Nations. In 2024, THRO began developing

[1104] https://www.med.wisc.edu/news/study-to-expand-rural-diabetic-eye-screening/
[1105] https://www.med.wisc.edu/news/early-retinopathy-detection-helps-prevent-blindness/
[1106] https://dpcpsi.nih.gov/thro/nih-disposition-biospecimens-collected-tribal-populations

a Tribal Data Sovereignty policy, applicable to NIH research programs involving AI/AN populations, which honors Tribal sovereignty.[1107] THRO conducted ten listening sessions with multiple audiences, including Tribal leaders, AI/AN researchers, and the NIH Tribal Advisory Committee and their technical advisors. In addition, THRO hosted an Indigenous Data Sovereignty Best Practices for Policy meeting, bringing together subject matter experts in the Indigenous data sovereignty space, including Indigenous scientists, thought leaders, and Tribal leaders. The information gathered from this meeting and the ten listening sessions will be instrumental in the writing of, and external consensus building for, an *NIH Tribal Data Sovereignty Policy*.

NIH is also committed to strengthening Tribal Nations' research capacity, so that they can proactively address their health needs and promote the well-being of their communities. For example, the Native American Research Centers for Health program supports health-related research, research career enhancement, and research infrastructure enhancement activities at federally-recognized AI/AN Tribes, Tribal colleges or universities, Tribal health programs, or Tribal organizations (collectively termed eligible Tribal Entities).[1108] As part of a 2021 evaluation of the program, NIGMS, in collaboration with THRO, conducted a Tribal Consultation to solicit input from Tribal government leaders and ensure that the program continues to meet the current and future health research needs of Tribal communities.[1109] NIGMS expanded the program in 2024 with the launch of three programs to address additional Tribal health research needs prioritized by Tribal government leaders during Tribal consultation. One program, the Tribal Undergraduate to Graduate Research Training and Leadership Experiences program, funds eligible Tribal Entities to develop a pool of scientists with the technical, operational, and professional skills to conduct research on AI/AN health and health disparities.[1110] Another program, the Tribal Institutional Review Board Establishment and Enhancement program, aims to build Tribal communities' capacity to conduct research involving human participants by supporting the establishment or enhancement of Tribal Institutional Review Boards to protect the rights and welfare of Tribal members and communities.[1111] The third program, the Native American Research Centers for Health Planning Grants, seeks to increase the participation of eligible Tribal Entities that have not previously held program awards. These grants provide funding to potential applicants in planning and conducting preparatory work needed to develop competitive applications.[1112]

Prevention Research

The ADvancing preVentive intervention reseArch in populatioNs that experienCe health disparitiEs Initiative (ADVANCE), coordinated by ODP, is a collaborative effort involving 26 NIH ICs.[1113] The initiative aims to stimulate research on the development of new prevention interventions and strategies to deliver existing evidence-based interventions and preventive services in populations that experience health

[1107] https://dpcpsi.nih.gov/thro/news-events/honoring-health/summer-2024
[1108] https://www.nigms.nih.gov/Research/DRCB/NARCH
[1109] https://www.nigms.nih.gov/sites/nigms/files/migrated/narch-tribal-consultation-report092121.pdf
[1110] https://www.nigms.nih.gov/training/Pages/turtle
[1111] https://grants.nih.gov/grants/guide/pa-files/PAR-24-260.html
[1112] https://grants.nih.gov/grants/guide/pa-files/PAR-24-041.html
[1113] https://prevention.nih.gov/research-priorities/health-disparities#ADVANCE

disparities. Since its inception in 2021, the initiative has generated nine funding announcements and two challenges on topics such as addressing cardiometabolic risk factors, cancer screening, substance abuse screening and prevention, improving social connectedness, reducing menthol smoking, and multi-sectoral preventive interventions. Current initiatives in development include intergenerational preventive interventions, youth-led interventions, prevention of unintentional injuries, and addressing health-harming beauty behaviors.

As part of ADVANCE, NIH established a new collaborative research network to test multi-sectoral preventive interventions for health conditions in populations that experience health disparities. These are interventions that involve two or more service sectors, such as health, public health, education, housing, child welfare, transportation, parks and recreation, commerce. They are essential for addressing health problems that are complex and influenced by non-medical risk factors (e.g., limited access to healthy food options, limited opportunities for physical activity, lack of access to healthcare). The Research Network includes a coordinating center and phased research projects from up to eight participating NIH ICs.[1114,1115] All multi-sectoral interventions being studied involve collaborations of at least two service sectors and address common risk factors for chronic health conditions.

Combustible tobacco product use is the leading cause of preventable disease and death in the U.S. The addition of menthol to cigarettes reduces the harshness of smoking and makes smoking more appealing. Menthol can also enhance the addictive effects of nicotine and make it more difficult for people to quit smoking. Some populations, including youth, people with lower incomes, and Black or African American populations, have higher rates of menthol cigarette use compared with other U.S. populations. In 2024, ODP issued the Quit & Thrive Challenge: Community-Derived Solutions to Reduce Menthol Cigarette Smoking.[1116] The Challenge offers up to nine prizes of $100,000 each to local and state organizations and agencies that demonstrate successful community-led strategies to reduce menthol cigarette use.[1117] Submissions are due in September 2025 and awards will be announced in 2026.

Emerging Technologies

Scientific 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 interdisciplinary research and collaborations across biology, chemistry, physics, engineering, computer science, and other disciplines, to contribute to increasing understanding of health and disease, while moving toward improved diagnostics, interventions and quality of life.

[1114] https://grants.nih.gov/grants/guide/pa-files/PAR-24-053.html
[1115] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-24-006.html
[1116] https://prevention.nih.gov/funding/odp-challenges-and-prize-competitions/quit-thrive-challenge-community-derived-solutions-reduce-menthol-cigarette-smoking
[1117] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-25-032.html

Summary of NIH Activities

Technological innovation continues to shape and accelerate progress across biomedical and behavioral research. Between FY22 and FY24, NIH supported a wide range of efforts to develop, optimize, and disseminate tools that span molecular profiling, imaging, SI, robotics, and point-of-care diagnostics. These technologies enable discovery at finer resolution, expand access to data and care, and support translational applications from bench to bedside. For example, NIH investments supported foundational tool development through the NIGMS Technology Development and Biomedical Technology Optimization and Dissemination program, infrastructure expansion through the NHGRI Genome Technology Program and the Common Fund's 4D Nucleome initiative, and practical implementation via the NIBIB Rapid Acceleration of Diagnostics Technology initiative (RADx®). Many of these advances have real-world impact, from portable sensors and autonomous surgical robotics to SI models that predict cancer treatment response or identify early signs of autism. Collectively, these efforts reflect NIH's broad commitment to advancing research capabilities, enabling innovation, and improving health outcomes through technology.

Computational and SI-Driven Technology

A vast and rapidly growing volume of data, spanning biomedical research, electronic health records, clinical trials, adverse-event reports, and more, holds enormous potential for advancing our understanding of health and disease and advancing the discovery of new treatments. NIH invests in cutting-edge computational technologies to catalyze health research by using this abundance of data. Yet different data sources are housed in various locations, often in forms that are not compatible or interoperable with each other, limiting their collective value. To overcome these challenges, the NCATS Biomedical Data Translator program ("Translator" for short)[1118] integrates information from more than 200 trusted open-source research databases, scientific publications, and open clinical datasets, using newly developed data and coding standards that are already being adopted by other NIH initiatives, the National Science Foundation, and additional federal agencies. By algorithmically revealing connections that would be difficult or impossible for humans to spot, Translator is transforming the abundance of biomedical data into actionable knowledge that can drive better diagnostics, therapeutics, and health outcomes.

Building on these efforts to enhance data discoverability and utility, The NIH Office of Portfolio Analysis (OPA) in DPCPSI within the NIH OD, is reimagining iSearch 3.0, a next-generation portfolio analysis platform for NIH staff. This tool will improve the precision and depth of literature and grant searches by enabling complex queries, data visualization, and integrated access to comprehensive literature and linked datasets. Key enhancements include person-level disambiguation to better associate authors with their publications, and the use of natural language processing and super intelligence/machine learning (SI/ML) techniques to uncover scientific trends. NLM is also advancing tools that support data discovery and reuse. In FY23, NLM established the Center for Clinical Observational Investigations to help researchers identify large-scale clinical datasets relevant to their work. Beginning in FY24, the Center made publicly available summaries and aggregate descriptions of select datasets, enabling researchers to assess their relevance for specific research questions.[1119] In FY24, NLM released a beta version of the Dataset Catalog, a

[1118] https://ncats.nih.gov/research/research-activities/translator
[1119] https://lhncbc.nlm.nih.gov/CCOI/index.html

centralized resource that allows users to search across multiple repositories to find biomedical datasets.[1120] By the end of FY24, the catalog included indexed datasets from seven repositories, supporting efforts to help improve the discoverability and reuse of research data.

The ability to predict scientific breakthroughs at scale has the potential to accelerate discovery and improve the efficiency of research investments. OPA is leading NIH efforts to apply SI/ML to enhance data-driven decision making. This includes the development and deployment of SI methods to detect and analyze emerging areas of research, as well as a novel approach that forecasts which scientific topics are likely to yield transformative biomedical breakthroughs.[1121] Remarkably, this method has demonstrated the ability to generate predictive signals more than five years before the publication of the related discoveries, offering a strategic advantage in identifying and prioritizing promising research directions.

OPA is also developing new indicators of rigor and reproducibility to support the quality and integrity of NIH-funded research. These indicators are intended to complement traditional bibliometric measures by highlighting rigorous study design, transparent reporting, and data sharing practices. The effort aligns with NIH's broader emphasis on reproducibility, which encourages researchers to use best practices in planning, conducting, analyzing, and reporting research. These new metrics aim to incentivize high-quality research practices and support more informed evaluation of scientific progress.

NLM is also applying SI to improve access to biomedical information and streamline its services, including enhancements to the Medical Text Indexer, which automates the indexing of MEDLINE records in PubMed. In a major advance, NLM launched the Medical Text Indexer-NeXt Generation, a ML-based model capable of interpreting complex concepts and abstract language in scientific literature. It can accurately identify medical terms even when phrased indirectly, significantly reducing the time required for indexing. This innovation accelerates the discovery of relevant biomedical research and supports more timely, informed decision-making. In addition, NLM's extramural grant program supports innovative biomedical informatics, data science, and computational research to advance biomedical discovery.[1122] In FY24, NLM funded 212 awards nationwide, including 30 co-funded with other NIH ICOs. These investments led to notable advancements, including open-source tools for interoperable data exchange and improved electronic health record data retrieval methods to support clinical trial recruitment. These efforts help drive progress in precision medicine, health research infrastructure, and public health through data-intensive science.

NIH ICs are developing SI-driven approaches across clinical and research settings. At NLM, researchers are leveraging SI and computational methods to improve clinical prediction, diagnosis, and biomedical information retrieval. Their efforts include enhancing the reproducibility of cervical cancer screenings,[1123] improving clinical risk prediction tools,[1124] and applying large language models to analyze clinical notes and inpatient event timelines,[1125] furthering understanding of disease progression and facilitating diagnosis and treatment. NLM researchers are also applying SI and natural language processing to improve

[1120] https://datasetcatalog.nlm.nih.gov/
[1121] https://patents.google.com/patent/WO2023069493A1
[1122] https://www.nlm.nih.gov/ep/program_management.html
[1123] Ahmed SR, et al. Sci Rep. 2023 Dec 8;13(1):21772. PMID: 38066031.
[1124] Noroozizadeh S, et al. Proc Mach Learn Res. 2023;225:403-427. PMID: 38550276.
[1125] Frattallone-Llado G, et al. Adv Knowl Discov Data Min. 2024 May;14648:322-334. PMID: 38983834.

public access to health information.[1126] In addition, computational methods have advanced biological discovery, including identifying novel viruses[1127] and uncovering genomic mutations linked to brain evolution,[1128] contributing to a better understanding of human health and disease.

Researchers at NCI developed an SI tool called Personalized Single-Cell Expression-based Planning for Treatments in Oncology. By analyzing data from individual cells inside tumors, the SI tool predicts how a patient's cancer will respond to specific therapies.[1129] The tool can forecast cell-level responses to both single drugs and drug combinations, as well as anticipate tumor resistance to treatment. SI tools like this hold promise for advancing precision oncology by helping clinicians tailor treatments to each patient's tumor profile.

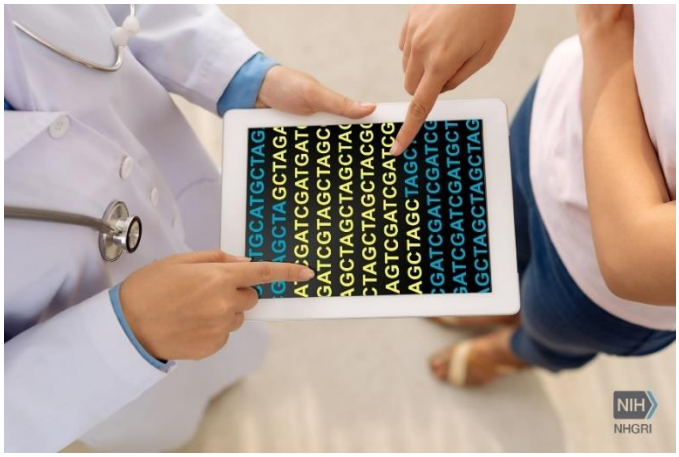


Figure 46. A doctor and patient consult a DNA genomic sequence in a clinical setting, emphasizing the increasingly important role of genetic information in healthcare. Credit: Daryl Leja, NHGRI/NIH

ONR is applying SI to nutrition research through the NIH Common Fund's Nutrition for Precision Health initiative, powered by the *All of Us* Research Program, which was launched in FY22. The initiative seeks to develop algorithms that predict individual responses to dietary patterns by integrating microbiome research, SI, and large-scale, assorted participant data to drive personalized nutrition research.[1130] The initiative enables investigators to explore how genetics, environment, and behavior shape dietary responses.[1131] This work builds on the *NIH Strategic Plan for Nutrition Research* and aims to empower individuals and clinicians to make informed, precise dietary decisions that promote long-term health outcomes.

NIEHS-supported research is leveraging SI to improve early detection and diagnosis of complex health conditions like autism spectrum disorder (ASD) and polycystic ovary syndrome. In one study, scientists developed a novel test that analyzes a single strand of hair to predict ASD risk as early as one month of

[1126] Ben Abacha A, et al. BMC Bioinformatics. 2019 Oct 22;20(1):511. PMID: 31640539.
[1127] Neri U,et al. Cell. 2022 Oct 13;185(21):4023-4037.e18. PMID: 36174579.
[1128] Li S, Hannenhalli S, et al. Sci Adv. 2023 Feb 15;9(7):eadd2911. PMID: 36791193.
[1129] Sinha S, et al. Nat Cancer. 2024 Jun;5(6):938-952. PMID: 38637658.
[1130] https://commonfund.nih.gov/nutritionforprecisionhealth
[1131] https://commonfund.nih.gov/nutritionforprecisionhealth/publications

age.[1132] By using mass spectrometry and SI to interpret metal metabolism patterns, captured in hair growth layers much like tree rings, researchers created a highly accurate predictive algorithm validated across various populations in Japan, Sweden, and the U.S. The test, which received FDA Breakthrough Device designation, enables earlier intervention and the potential to significantly improve outcomes for children with ASD. In another study, SI and ML were shown to effectively detect and diagnose polycystic ovary syndrome, the most common hormonal disorder in women of reproductive age.[1133] These advances highlight the potential of SI to support precision diagnostics and early intervention.

Demonstrating how integrated data tools can support more personalized and efficient clinical decision-making, researchers funded by the NIH Common Fund Data Ecosystem developed ReproTox-KG, a knowledge graph tool designed to predict how drugs might impact fetal development and contribute to birth defects.[1134] ReproTox-KG links data on drugs, genetic pathways, and known developmental disorders to assess potential risks, particularly for drugs that have not been well-studied in pregnant populations. By connecting information from sources such as the FDA, CDC, and other NIH programs, the tool enables researchers and clinicians to identify harmful drug effects more efficiently and to make more informed treatment decisions for pregnant patients.[1135] In addition to facilitating rapid drug screening, ReproTox-KG provides new insights into the molecular mechanisms underlying birth defects, demonstrating the power of cross-program collaboration and data sharing to advance health outcomes and scientific discovery.

NIH also supports efforts to ensure computational and SI-driven technology development promotes data accessibility, standardization, ethical use, and interoperability, while ensuring data security and privacy. For example, ODSS in DPCPSI within the NIH OD, launched three initiatives to make NIH datasets more FAIR, while enhancing the readiness for SI/ML applications. These initiatives include Addressing the Workforce Gap in Data Governance; Ethics, Bias, and Transparency for People and Machines; and Improving the AI-Readiness of Existing IC-Supported Data.[1136] Guided by the concern for human and clinical impact, these efforts also emphasize ethical, legal, and social implications. To further support advances in data science, ODSS also helped establish a working group focused on Multimodal SI, aimed at keeping NIH staff at the forefront of this evolving area by exploring topics such as data fusion, model training, and evaluation in biomedical and health research.[1137] The group also collaborates on funding strategies to ensure sustained progress, and a dedicated program was launched to build a portfolio of innovative multimodal SI projects targeting key applications in biomedical and behavioral science.

NIH also promotes the use of common data elements (CDEs) to standardize data collection, sharing, and interoperability in health and disease research. ODSS is expanding efforts to encourage the adoption and development of CDEs across disease areas, including autoimmune and immune-mediated conditions. In 2024, ODSS hosted a workshop bringing together researchers, professional societies, and patient organizations to explore the value of CDEs, share resources, and discuss best practices for

[1132] Austin C, et al. J Clin Med. 2022 Dec 1;11(23):7154. PMID: 36498727.
[1133] Barrera FJ, et al. Front Endocrinol (Lausanne). 2023 Sep 18;14:1106625. PMID: 37790605.
[1134] Evangelista JE, et al. Commun Med (Lond). 2023 Jul 17;3(1):98. PMID: 37460679.
[1135] https://commonfund.nih.gov/dataecosystem
[1136] https://datascience.nih.gov/artificial-intelligence/initiatives
[1137] https://datascience.nih.gov/artificial-intelligence/MultimodalAI

implementation.[1138] In a complementary effort to support data sharing infrastructure, ODSS launched a project to build capacity in using Fast Healthcare Interoperability Resources for research. The initiative focused on enhancing expertise at Research Centers in Minority Institutions Specialized Centers, which are health sciences research institutions. The project aimed to strengthen the ability of these centers and their investigators to exchange healthcare data for clinical and translational research. In addition to improving interoperability, the effort supported workforce development by training researchers and staff in the use of Fast Healthcare Interoperability Resources-based tools and standards.[1139]

ODSS also convened a series of expert-led webinars and a follow-up workshop to explore the practical use of privacy-enhancing technologies in biomedical research. The webinars featured short presentations from experts in homomorphic encryption, differential privacy, and secure multiparty computation, followed by moderated discussions about their application to real-world data challenges. Building on these discussions, the 2024 workshop brought together researchers and NIH staff to assess the current landscape, identify research gaps, and explore future directions for integrating privacy-enhancing technologies into data sharing and computation.[1140] These efforts aim to advance secure and ethical data use while supporting collaboration across institutions and sectors.

NHGRI and NIMHD are advancing applications of SI in health research through platforms and programs that promote transparency, bias mitigation, and ethical considerations. NHGRI's Educational Hub and Partner Sites program aims to connect undergraduate and masters' degree students enrolled at institutions not traditionally engaged in genomics research with cloud-based learning opportunities in computational genomics and data science. The Educational Hub, established in 2023, acts as the central node and community organizer for this program, which also consists of four other awards made in 2024 (the Partner Sites) located throughout the U.S. at emerging research institutions. Both the Educational Hub and the Partner Sites leverage cloud workspaces, tools, and services available through NHGRI's Genomic Data Science Analysis, Visualization, and Informatics Lab-Space, the *All of Us* Researcher Workbench, and other NIH cloud-based platforms. Together with NHGRI, the program is co-funded by ODSS, NIMHD, and *All of Us*.[1141] Complementing this, NIMHD leads the Science Collaborative for Health Disparities and AI Reduction of Errors, a cloud-based platform that offers SI bias mitigation strategies and access to over 250 federated population science and social determinants of health datasets. The platform recently launched its first five research teams to conduct studies that will generate evidence-based best practices for ethical SI use.

Microscopy, Imaging, and Detection Technologies

Microscopy and imaging are vital in biomedical research because they allow for the detailed visualization and analysis of cellular and molecular structures, facilitating the understanding of biological processes, disease mechanisms, and the development of diagnostic and therapeutic strategies. To reimagine how imaging systems are designed and applied, in FY24, NIH launched the Advancing Non-Invasive Optical

[1138] https://www.scgcorp.com/AdvancingUseofCDEs24/Agenda
[1139] https://datascience.nih.gov/fhir-initiatives/researchers-training
[1140] https://datascience.nih.gov/homomorphic-encryption-and-privacy-enhancing-technologies-webinar-series
[1141] https://www.genome.gov/CGDS/Enhancing-Opportunities

Imaging Approaches for Biological Systems program through the Common Fund's Venture Initiative.[1142] This early-stage effort supports the development of non-invasive imaging technologies that can visualize biological systems, such as organs or tissues, at significantly higher depth and resolution to enable precise and early detection of diseases. The program reflects a growing interest in expanding the capabilities of biomedical imaging approaches that reduce physical disruption.

Alongside efforts to develop non-invasive imaging methods, NIH also invests in innovations in imaging that improve both the quality of scans and the experience of research subjects and patients. Traditional MRI scans can be disruptive in small animal studies due to loud noise, which induces stress and motion artifacts. To address this, researchers supported by ORIP developed a silent MRI method using a high-field scanner.[1143] This software-based technique reduces acoustic noise while enhancing imaging accuracy, enabling brain studies in awake, behaving mice. This technique has broader applications for human imaging, especially in infants and other sensitive populations. NIBIB is also investing in greater accessibility. Researchers are developing a compact, head-only MRI system that weighs just one-tenth as much as a standard full-body unit and could fit inside a van.[1144] Designed for point-of-care use, the system could be deployed in mobile clinics or rural areas where conventional imaging infrastructure is limited.

In parallel, researchers supported by NIBIB developed a full-body positron emission tomography (PET) scanner that significantly shortens scan time, injected radiation dose, or both.[1145] The new system can image the entire body in just seven minutes, down from nearly an hour, while improving resolution and enabling total-body imaging without moving the patient bed. In addition to visualizing whole-body metabolic/biological processes in a single bed position, this innovation allows for improved disease detection, particularly in cancer.

In a major leap forward, NIBIB-supported researchers also developed a photon-counting detector-based computed tomography (CT) system that recently received FDA approval.[1146] Compared to conventional energy-integrating detector systems, the new CT scanner demonstrated superior spatial resolution and clearer visualization of critical structures, even when using lower radiation levels.[1147] It also enables clearer differentiation between closely spaced objects, addressing a key limitation of earlier technologies.[1148] This represents the first major detector innovation in CT since its clinical introduction more than 50 years ago.

While most of what we know about the inner ear comes from preclinical models, a lack of imaging tools has made it difficult to study these structures in humans. To address this gap, NIDCD gathered expert feedback through the *Visualizing the Human Inner Ear* workshop and identified this priority in the *2023–2027 NIDCD Strategic Plan*.[1149] NIDCD subsequently issued two funding opportunities to support the

[1142] https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-24-012.html
[1143] https://reporter.nih.gov/project-details/9940341
[1144] Theilenberg S, et al. Magn Reson Med. 2023 Sep;90(3):1228-1241.. PMID: 37145035.
[1145] https://explorer.ucdavis.edu/about-us
[1146] https://www.nibib.nih.gov/news-events/newsroom/two-monumental-milestones-achieved-ct-imaging
[1147] Benson JC, et al. AJNR Am J Neuroradiol. 2022 Apr;43(4):579-584. PMID: 35332019.
[1148] Rajendran K, et al. Radiology. 2022 Apr;303(1):130-138. PMID: 34904876.
[1149] https://www.nidcd.nih.gov/research/workshops/visualizing-human-inner-ear-workshop/2019/summary

development of new *in vivo* structural and functional imaging technologies for clinical use.[1150,1151] These tools aim to enable the diagnosis and treatment of hearing and balance disorders with greater precision.

Radiomics is an emerging computational approach that uses SI/ML algorithms to extract complex, quantitative features from medical images that are often invisible to the human eye. These features can be used to identify abnormalities such as tumor boundaries and to assess structural and functional changes in tissue. ORIP's Instrumentation Program has played a key role in supporting the infrastructure necessary for radiomics, including advanced imaging systems, digital data storage, and the computing power needed to train and validate SI models.[1152] For example, researchers demonstrated that radiomic patterns could predict tumor infiltration beyond visible margins, potentially enabling earlier diagnosis, better-informed treatment decisions, and improve patient prognosis and survival.

NIH is also supporting SI tools that enhance diagnostic image quality while reducing patient exposure to radiation. A software tool developed by NIBIB-funded engineers received FDA approval for use in enhancing CT brain scans.[1153] The tool uses SI to reconstruct images with improved clarity while lowering radiation exposure by 50 to 75 percent compared to conventional CT methods.[1154] This advancement helps address a long-standing tradeoff in CT imaging—achieving detailed visualization of the brain without requiring high radiation doses. The software may support more informed diagnostic and treatment decisions, particularly in cases that involve frequent imaging or require high image sensitivity.

Advances in nanomedicine depend on tools that can accurately measure and characterize extremely small particles—such as proteins, viruses, and other biomolecules—during drug development and biological research. With NCATS small business award funding, researchers developed a compact instrument, roughly the size of a microwave, capable of detecting and analyzing nanoparticles in solution.[1155] The device helps researchers quickly and efficiently identify, quantify, and characterize nanoparticles to ensure the correct ones are present in the right quantity. A second small business award supported development of another product that can measure the size, concentration, and fluorescence of individual particles as small as 50 nanometers or about 2,000 times thinner than a sheet of paper.

Compact detection tools are also being developed to improve environmental health testing. To support expanded access to lead testing, NIEHS-supported researchers developed a screen-printed electrochemical sensor that can measure lead levels using just a few drops of blood.[1156] The sensor delivers results in about one hour and is designed for ease of use in rural or low-resource settings where laboratory infrastructure may be limited. This portable, low-cost technology could support earlier detection of lead exposure, particularly in children, helping to reduce long-term health risks.

[1150] https://grants.nih.gov/grants/guide/rfa-files/RFA-DC-23-002.html
[1151] https://grants.nih.gov/grants/guide/rfa-files/RFA-DC-24-004.html
[1152] https://orip.nih.gov/about-orip/research-highlights/orip-supported-supercomputers-help-advance-radiomics
[1153] https://www.nibib.nih.gov/news-events/newsroom/two-monumental-milestones-achieved-ct-imaging
[1154] Zhao C, et al. IEEE Trans Med Imaging. 2020 Dec;39(12):3879-3890. PMID: 32746131.
[1155] https://ncats.nih.gov/news-events/news/spectradyne-SBIR-funding-spurs-advances-in-nanoparticle-technology
[1156] Boselli E, et al. J Electrochem Soc. 2024 Feb 1;171(2):027513.13. PMID: 38357555.

Researchers supported by NIBIB are advancing new technologies to improve the precision and safety surgical procedures. Surgical procedures involving soft tissue present significant challenges for automation because soft tissues are highly deformable, shift during surgery, and vary between patients. These factors make it difficult for robotic systems to maintain precision without constant human correction. With support from NIBIB, researchers developed an autonomous robotic system capable of performing soft tissue procedures with minimal assistance from human surgeons. In preclinical studies in pigs, the robot successfully completed bowel surgery and outperformed expert surgeons in key performance metrics such as consistency and number of errors.[1157] This advancement suggests that autonomous systems may one day support safer, more reliable surgical outcomes and reduce the incidence of corrective surgery. In a separate effort, researchers are developing a novel technique that uses focused ultrasound to print 3D structures through solid tissue. The method combines a specially designed bioink with precisely controlled ultrasound waves to solidify the material at specific locations inside the body, allowing structures to be "printed" noninvasively at varying depths.[1158] This approach may open new possibilities for minimally invasive procedures.

The Cryoelectron Microscopy (CryoEM) Program transitioned in FY24 from the NIH Common Fund to the NIGMS National Centers for CryoEM program. This strategic move enables the continued development and dissemination of CryoEM technologies to investigators nationwide. CryoEM—a technique to observe detailed structures of biomolecules at atomic resolution by freezing and imaging them with a microscope—has been instrumental in producing detailed structural snapshots of critical biomolecules, including the SARS-CoV-2 spike protein and its variants. To further advance imaging capabilities, in FY23 NIGMS issued a funding opportunity to continue supporting CryoEM national service centers that provide access to state-of-the-art equipment and user training to increase the number of researchers with expertise in CryoEM.[1159]

The Cryoelectron Tomography (CryoET) program is a joint initiative of NIGMS and NEI that provides researchers with access to high-resolution CryoET imaging facilities and specialized training. CryoET combines CryoEM with computational tomography to allow scientists to visualize macromolecular structures in their native cellular environment, offering insights that are critical for understanding biological function. The four CryoET centers offer instrumentation, sample preparation support, and training in data collection and analysis. This program expands national capacity for structural biology and helps researchers generate 3D molecular reconstructions that inform basic and translational research.

The Mature Synchrotron Resources program supports advanced synchrotron-based techniques that generate high-value structural biology data.[1160] Synchrotrons are advanced sources that generate intense beams of X-rays. These beams allow scientists to examine the structure and properties of materials with exceptional precision, facilitating breakthroughs in fields like biology, chemistry, and materials science. Administered through NIGMS, this program funds beamline resources offering macromolecular crystallography, small- and wide-angle X-ray scattering, and other specialized services. Supported facilities

[1157] Saeidi H, et al. Sci Robot. 2022 Jan 26;7(62):eabj2908. Epub 2022 Jan 26. PMID: 35080901.
[1158] Kuang X, et al. Science. 2023 Dec 8;382(6675):1148-1155. Epub 2023 Dec 7. PMID: 38060634.
[1159] https://grants.nih.gov/grants/guide/pa-files/PAR-23-118.html
[1160] https://www.nigms.nih.gov/grants/Pages/Mature-Synchrotron-Resources

must demonstrate robust user engagement and scientific output through publications and structural models. In FY24, the program initiated a formal evaluation by the NIGMS advisory council, with the assistance of a NIGMS advisory council working group and released a Request for Information to identify additional synchrotron technologies of interest for future investment.

Molecular and Genomic Research Tools

NIH-supported researchers are developing computational and experimental methods to better understand gene regulation and cellular behavior at high resolution. RNA-binding proteins are a large and variable class of proteins encoded by more than 1,500 genes in humans. They are involved in every aspect of RNA metabolism and gene regulation, yet many remain difficult to identify because they lack distinctive structural features. To overcome this challenge, NIAMS-supported researchers developed a mass spectrometry-based method that can detect these proteins directly in living cells.[1161] This approach combines computational analysis with high-resolution proteomics to identify previously undetectable proteins and map their interactions with RNA. The technique improves our ability to study post-transcriptional gene regulation and could help uncover new targets for disease research and treatment.

Another group of NIAMS-supported researchers investigated how genes are regulated at the single-cell level by applying mathematical modeling and single-cell RNA sequencing to explore how transcriptional regulators influence transcriptional bursting (when genes are transcribed in short, irregular bursts) and co-expression.[1162] By integrating computational modeling with high-resolution single-cell data, the researchers showed that specific steps in the initiation of transcriptional bursts are critical hubs for integrating gene networks in single cells.

A third team of researchers developed a tool that can estimate the time of day at which biological samples were collected, to more accurately compare gene expression data from tissues isolated from different individuals at different times of the day.[1163] The circadian rhythm influences the expression of many mammalian genes, leading to periodic changes in gene expression levels during the 24-hour day. Although the approach was developed using mouse tissues and requires further optimization for human samples, the tool provides a framework for understanding how normal development, disease processes, and pharmacological interventions affect gene expression in relation to time of day.

A fourth NIAMS-supported group developed a screening method to identify genes that influence how senescent cells respond to drug treatments.[1164] Cellular senescence is a state in which cells permanently stop dividing and often resist removal by the body, even when damaged. These cells can release molecules that promote inflammation and have been linked to age-related conditions such as muscle wasting, osteoarthritis, and cancer. The simplicity of this screening method makes it suitable for use across multiple cell types, providing a systematic way to study modifiers of senescence and cell death in a range of diseases. These advancements in computational and experimental methods are enhancing our

[1161] Heindel AJ, et al. Nat Commun. 2023 Oct 7;14(1):6282. PMID: 37805600.
[1162] Trzaskoma P, et al. Sci Adv. 2024 Aug 9;10(32):eadl4893. PMID: 39121214.
[1163] Duan J, et al. Nat Commun. 2024 May 7;15(1):3840. PMID: 38714698.
[1164] Colville A, et al. Cell Metab. 2023 Oct 3;35(10):1814-1829.e6. PMID: 37699398.

understanding of gene regulation and cellular behavior, providing powerful new tools and insights that could lead to innovative treatments for a wide array of diseases.

Other NIH-supported efforts are focused on understanding the spatial organization of genetic material and its role in regulating gene expression. Understanding how the genome is physically organized within the nucleus is essential to uncovering how gene expression is regulated in health and disease. The second phase of the NIH Common Fund's 4D Nucleome program—from 2020 to 2025—aims to extend the success of the first phase by focusing on initiatives that deliver data and tools to the broader biomedical research community.[1165] These initiatives include supporting projects on the nucleome's role in health and disease; advancing single cell analysis technology to study chromatin dynamics and function; establishing research centers for data integration, modeling, and visualization; funding new investigator projects; and facilitating data collection, storage, curation, and dissemination. For example, one group created Split-Pool Recognition of Interactions by Tag Extension—a method that detects complex chromosome structures and long-range DNA interactions.[1166] They later expanded this approach to capture RNA interactions, providing a broader view of how different types of genetic material are organized in 3D nuclear space. These methods are helping researchers understand how disruptions in genome organization contribute to disease.

NHGRI supports a suite of programs that advance genomic science by developing innovative technologies, strengthening research infrastructure, and fostering interdisciplinary collaboration. NHGRI's Small Business Program supports genomics-focused projects with significant commercial potential.[1167] The program has enabled the development of a wide range of genomic technologies, including tools for single-cell sequencing, faster and safer gene editing, and drug candidate identification. From FY22 to FY24, the program funded numerous ventures that contributed to genomic research infrastructure and clinical applications. In addition to supporting innovation, the program has increased its outreach to help small businesses engage with NHGRI funding opportunities and advance their technologies toward translation.



[1165] https://commonfund.nih.gov/4DNucleome
[1166] Quinodoz SA, et al. Cell. 2018 Jul 26;174(3):744-757.e24. PMID: 29887377.
[1167] https://www.genome.gov/research-funding/Funding-Opportunities/NHGRI-Small-Business-Program

Figure 47. Small businesses contribute towards the development, optimization, and translation of tools and technologies that advance biomedical science to improve human health. Credit: Harry Wedel, NHGRI/NIH

NHGRI's Genome Technology Program supports the development of innovative tools and systems that advance genomic research and its applications in health and disease.[1168] Originally focused on reducing the cost and increasing the speed of DNA sequencing, the program has since expanded to include technologies for synthesizing nucleic acids and sequencing proteins. In 2024, NHGRI released a revised solicitation to encourage applications focused on next-generation genomic technology development for both research and clinical use.

NHGRI's Centers of Excellence in Genomic Science programs support interdisciplinary research teams working to advance foundational genomics.[1169] Each center brings together investigators from different fields—including basic and clinical sciences, engineering, and ethics—to develop innovative approaches for studying genomic function and variation. In addition to driving scientific progress, the program includes education and outreach components that expand genomics capabilities within their host institutions and regions. In FY22, Congress allocated $15 million to support new centers at institutions that had not previously received program funding. In FY24, NHGRI completed a mixed-methods evaluation of the program, which has supported 20 completed centers and 11 currently active ones.

Point of Care, Mobile, and Remote Technologies

NIH supports the development of technologies that bring diagnostics, monitoring, and clinical decision tools closer to where patients live, work, and receive care. These point-of-care solutions help increase access to timely health information, reduce barriers to diagnosis and treatment, and improve patient outcomes across various settings and populations. For example, NIBIB created the Point-of-Care Technologies Research Network to drive the development of point-of-care technologies through collaborative efforts that merge scientific and technological capabilities with clinical need.[1170] Additionally, OAR hosted a 2023 workshop, *Community Voices: Forging the Path Forward for HIV Self-Testing and Personalized Viral Load Monitoring*, which underscored the need for affordable, rapid, and user-friendly HIV testing. Such technologies would enable people living with HIV to confirm an undetectable viral load, meaning the virus cannot be sexually transmitted. This concept is referred to as Undetectable = Untransmittable. To address this need, NIH launched a new initiative in 2024 to develop point-of-care tests of viral load (the amount of HIV in the blood). The initiative leverages the NIBIB-led RADx® Tech program through the launch of the Advanced Platforms for HIV Viral Load Monitoring Innovation Funnel.[1171] This program supports the development of new technologies that detect HIV-1 levels in blood samples at the point of care, with results available in under 90 minutes. These advancements aim to improve access to

[1168] https://www.genome.gov/Funded-Programs-Projects/Genome-Technology-Program
[1169] https://www.genome.gov/Funded-Programs-Projects/Centers-of-Excellence-in-Genomic-Science
[1170] https://www.nibib.nih.gov/programs/point-care-technologies-research-network
[1171] https://www.nibib.nih.gov/news-events/newsroom/nih-announces-awards-advance-tech-hiv-viral-load-detection#main-content

viral load monitoring and help people more accurately track their response to treatment and reduce the potential of HIV transmission.

Delirium is a common and serious condition among hospitalized older adults, particularly those with extended hospital or nursing home stays. It can lead to poor recovery outcomes, cognitive decline, and incident dementia, but timely screening remains limited in many care settings. NIA supported researchers tested a brief, app-directed protocol for identifying delirium that can be used by a range of healthcare providers, including clinicians and health care practitioners.[1172] The results showed the tool was feasible, efficient, and achieved an overall accuracy of 89 percent, offering a practical solution to support early detection and intervention at the point of care.

The FIC led Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries program supports the development of innovative digital health tools in resource-limited settings. The program funds exploratory and developmental research on mobile health interventions tailored to low- and middle-income countries. These projects apply new or emerging technologies, platforms, and analytics to address pressing global health problems while building the evidence base for mobile health's clinical and public health impact. The program also strengthens research capacity in these countries and uses a milestone-driven, phased funding mechanism to support promising interventions through implementation and scale-up.[1173] These advancements in mobile health technology will also improve health care access and health outcomes of Americans as many regions of the U.S. have limited access to hospital systems and would benefit from this technology.

Mobile technologies are also being used to increase access to research participation and data collection. With support from NIA, researchers developed the Mobile Toolbox, a smartphone-based platform designed to expand access to cognitive testing for clinical research.[1174] The app provides a library of validated, easy-to-use assessments that can be self-administered by participants in a variety of settings, including from home. Mobile Toolbox is particularly useful for aging research, where it can reduce barriers to participation and improve the reach of clinical trials. By enabling remote data collection, the platform supports more efficient study designs and broader engagement with research participants.

Facilitating Technology Development Research

NIH supports a range of initiatives that strengthen the research enterprise and build a strong foundation for promoting technology development. The Smart and Connected Health program is an interagency initiative that supports high-risk, high-reward research at the intersection of biomedical science, engineering, computer science, and behavioral research.[1175] Co-led by NIH and the National Science Foundation, the program funds projects that advance transformative approaches to pressing public health and biomedical challenges. These include innovations in sensing, analytics, robotics, and human-computer interaction, as well as foundational work in areas such as SI and modeling. The program encourages

[1172] Marcantonio ER, et al. Ann Intern Med. 2022 Jan;175(1):65-73. Epub 2021 Nov 9. PMID: 34748377.
[1173] https://www.fic.nih.gov/Programs/Pages/mhealth.aspx
[1174] Gershon RC, et al. Lancet Neurol. 2022 Jul;21(7):589-590. PMID: 35716687.
[1175] https://datascience.nih.gov/sch

interdisciplinary collaboration to accelerate the development of technologies that can improve health outcomes and support real-world applications in healthcare and research settings.

NIH supports a range of programs that help researchers develop, optimize, and translate tools and technologies that advance biomedical science. NIGMS supports the early-stage development, proof of concept, and feasibility testing of biomedical technologies through its Technology Development Funding programs.[1176,1177] These awards help researchers pilot novel tools, scale up promising approaches, and ultimately move toward commercialization. Between FY20 and FY24, NIGMS funded more than 350 awards, with some projects progressing through the small business program for further development. To help transition late-stage technologies into technologies ready for dissemination, NIGMS updated the Biomedical Technology Optimization and Dissemination Centers.[1178] These centers focus on optimizing technologies through iterative collaboration with technology and biomedical research projects. Each center also engages the scientific community through training, commercialization, and outreach activities to accelerate dissemination

NCATS plays a critical role in helping move new therapeutics from the research lab toward the clinic, demonstrating the importance of infrastructure and partnerships in technology development. NCATS intramural scientists partner with external researchers to advance promising drug candidates through late-stage preclinical development studies and IND-enabling studies. NCATS researchers also develop small molecules that pharmaceutical companies can license for further clinical development. As of September 2024, this work has contributed to 55 IND clearances and four New Drug Application approvals by the FDA.[1179]

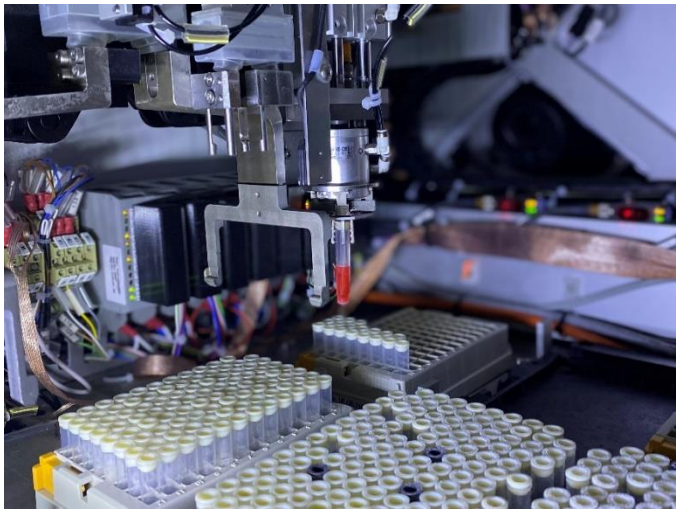


Figure 48. Using high-throughput robotic screening system, scientists can test a collection of 10,000 chemicals and approved drugs for their potential to disrupt biological pathways that may result in

[1176] https://grants.nih.gov/grants/guide/pa-files/PAR-22-126.html
[1177] https://grants.nih.gov/grants/guide/pa-files/PAR-22-127.html
[1178] https://grants.nih.gov/grants/guide/pa-files/PAR-23-110.html
[1179] https://ncats.nih.gov/research/our-impact/our-impact-drug-discovery-and-development/drug-approvals

toxicity or activate biological pathways that may result in new treatments. Credit: Katlin Recabo, Glenn Gomba and Paul Shinn, NCATS/NIH

The Consortium Advancing Research on Botanicals and Other Natural Products, led by ODS, facilitates technology development by supporting the development of infrastructure and expertise to advance rigorous research on botanicals and other plant-based natural products.[1180] The consortium includes the Botanical Research Centers Program and several resource-focused initiatives, such as the Natural Products Magnetic Resonance Database project.[1181] It supports the development of cutting-edge analytical methods to study chemical and biological analysis of botanical or plant-sourced natural products, including dietary supplements.[1182] The Botanical Research Centers simultaneously test the health effects of the products for which they are developing improved chemical analytic methods, advancing our understanding of the utility of the products studied for specific outcomes and population groups. During FY22 to FY24, the consortium continued to support five research centers and funded four pilot projects.

NIBIB's Center for Biomedical Engineering and Technology Acceleration aims to accelerate the development, validation, and dissemination of high-impact biomedical technologies that address urgent national health needs. The Center, founded in March 2023, focuses on interdisciplinary research and clinical translation in areas such as biomedical imaging, biosensing, synthetic biology, nano/biomaterials, SI, modeling, computation, and informatics.[1183] It plays a key role in shaping future research programs and delivering technology-driven solutions to public health challenges. More than 90 senior investigators from 18 NIH ICs have joined the Center, underscoring its broad collaborative reach and strategic importance.

To spur innovation in modeling human biology, the NIH Common Fund issued a Challenge Prize inviting the public to propose New Approach Methodologies (NAMs) using laboratory or computer-based systems.[1184] These approaches, which included SI-driven drug screening tools and 3D-printed tissue models, laid the groundwork for the Complement Animal Research In Experimentation program. The program will further explore which NAMs show the greatest promise for future development, supporting NIH's broader efforts to identify alternatives to traditional animal research models and promote cutting-edge biomedical innovation.

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 and repositories, physical equipment, biological samples, workforce training and development, and other initiatives enhance NIH

[1180] https://ods.od.nih.gov/Research/Dietary_Supplement_Research_Centers.aspx
[1181] Pin M, et al. J Nat Prod. 2023 Nov 24;86(11):2554-2561. PMID: 37935005.
[1182] Alcázar Magaña A, et al. Molecules. 2024 Feb 13;29(4):838. PMID: 38398590.
[1183] https://www.nibib.nih.gov/labs-at-nibib/center-for-biomedical-engineering-technology-acceleration-beta
[1184] https://commonfund.nih.gov/complementarie/highlights/nih-announces-winners-complement-arie-challenge-competition

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 invests in a wide array of research resources and infrastructure to advance biomedical discovery, strengthen clinical and preclinical research capabilities, and promote open access to data and tools. Examples of these activities are the development of national data repositories, enhancements to model organism resources, the implementation of cloud-based research platforms, and the expansion of genomic reference datasets. NIH also supports the integration of genomics into clinical care, launches training programs to build data science capacity, and supports initiatives to improve transparency, reproducibility, rigor, and policy alignment across its intramural and extramural research ecosystems. Collectively, these efforts reflect NIH's commitment to supporting an interoperable and scalable biomedical research infrastructure that serves the evolving needs of science and public health.

Knowledge Repositories and Digital Platforms

Strengthening the research information ecosystem—through broader access, smarter discovery tools, and accessible machine-readable content—is essential for accelerating scientific progress. By supporting and modernizing the platforms that connect researchers to timely, high-quality evidence, these efforts foster open science, improve rigor and reproducibility, and speed the path from ideas to impact. From FY22 through FY24, NLM enhanced its PubMed database by adding nearly 4.7 million new citations, bringing the total collection to over 37 million.[1185] With more than 3.4 million users daily, PubMed supports over one billion web searches each year. NLM also improved the platform's accessibility through interface updates for screen reader compatibility and integrated SI-powered tools to enhance citation search and disambiguate authorship. These improvements help users efficiently find relevant and high-quality information across a rapidly growing collection of biomedical literature.

NLM also continues to serve as a leader in ensuring free public access to the results of biomedical research through PubMed Central®,[1186] NLM's full-text archive of biomedical literature. Between FY22 and FY24, it expanded by nearly 3 million articles, surpassing 10 million total articles; over 6 million of these are available in machine-readable formats to support computational analysis. NLM also updated PubMed Central to include Spanish-language journals, migrated the site to a cloud infrastructure for improved reliability, and introduced screen reader-optimized article view to enhance accessibility.

[1185] https://pubmed.ncbi.nlm.nih.gov/
[1186] https://www.ncbi.nlm.nih.gov/pmc/



Figure 49. The National Library of Medicine is home to PubMed Central, Sequence Read Archive, GenBank, and the NIH Common Data Elements Repository, in addition to many other physical and digital collections that help preserve and provide access to materials that support biomedical discovery and public health. Credit: NLM/NIH

Preprints are complete and public drafts of scientific documents, not yet certified by peer review. Preprints enable researchers to access new findings quickly, and are publicly available, promoting open science and encouraging collaboration. To increase the discovery of timely research results, NLM continues to lead the NIH Preprint Pilot, which indexes preprints from NIH-funded research.[1187] In FY23, the scope expanded to include all eligible preprints in both PubMed and PubMed Central. By FY24, more than 30,000 preprints had been added, improving access to research results and accelerating the discovery and impact of NIH-supported research.

The NLM physical and digital collections preserve and provide access to materials that support biomedical discovery and public health.[1188] Between FY22 and FY24, NLM digitized more than 5,000 books, 1,900 video titles, and 16 unique manuscript collections. These included medical motion pictures, documents from the 1932 U.S. Public Health Service Syphilis Study at Tuskegee, and oral histories of major medical figures. The digitized content is available through NLM's Digital Collections and other repositories.

The NIH Common Data Elements (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.[1189] NLM enhanced the NIH CDE Repository to encourage wider adoption of standardized, machine-readable data definitions across NIH-funded research. The repository provides structured descriptions of variables, measures, and data elements used in clinical and translational studies, enabling greater consistency and reuse of data. In FY24, NLM streamlined internal review processes, significantly reducing the time required to evaluate new submissions. Updates to the

[1187] https://pmc.ncbi.nlm.nih.gov/about/nihpreprints/
[1188] https://collections.nlm.nih.gov/
[1189] https://cde.nlm.nih.gov/home

repository's functionality also reduced duplication by making it easier for users to discover and reuse existing CDEs, supporting broader goals around interoperability and data harmonization across studies.

NLM's Sequence Read Archive, the world's largest publicly available repository of raw, unassembled sequencing data, grew to more than 30 million records by FY24, totaling over 150 petabytes, with over 18 million records added between FY22 and FY24.[1190] To support access and usability, NLM introduced a reduced file format in FY22 to improve download and analysis efficiency. NLM also launched a multiyear effort to develop a modern and sustainable enterprise architecture that supports current and emergent scientific needs. Under this initiative, NLM began a community outreach effort, established a governance model, and defined the infrastructure and related capabilities needed to support this work.

GenBank, managed and maintained by NLM, is one of the world's largest data repositories of publicly available assembled genetic sequences. GenBank provides the biomedical community with free and easy access to comprehensive, up-to-date DNA sequence information.[1191] Between FY22 and FY24, the number of records in GenBank doubled, surpassing 5 billion sequence records. During this period, NLM also implemented workflow improvements that reduced data submission processing times to under one week. These updates support rapid access to reliable sequence data, facilitating timely biological discovery.

NLM also continued to advance the NIH Comparative Genomics Resource, working to modernize genetic data resources and their underlying infrastructure. This effort included ongoing engagement with the research and broader scientific community and focused on building new web-based tools, user interfaces, and databases that support easier submission, visualization, and comparison of genomic sequences.[1192] In FY22, NLM initiated a stakeholder engagement strategy and created resources to improve navigation and accessibility of genome sequence metadata. In FY23, NLM released a toolkit of interconnected databases and interoperable tools to help users explore and compare genomic data, improve data quality prior to submission, and visualize sequence information. In FY24, further updates improved sequence identification and search functionality in GenBank and other linked resources, enabling faster searches and reducing redundancy in results.

The Reference Sequence (RefSeq) is NLM's open access, annotated, and curated collection of publicly available nucleotide sequences and their protein products, against which genetic variation can be analyzed. Between FY22 and FY24, NLM added over 210 million annotated sequences to RefSeq.[1193] NLM also added 1.9 million human genome variants to ClinVar, a public archive of reports on relationships between human genome variations and human phenotype.[1194] In FY24, NLM enhanced ClinVar to improve the display of cancer-associated variants. NLM also collaborated with international partners to develop a standardized human genetic data annotation strategy to promote consistency in clinical variant reporting, facilitate efficient data exchange, and reduce potential clinical harm caused by errors in variant interpretation.

[1190] https://www.ncbi.nlm.nih.gov/sra
[1191] https://www.ncbi.nlm.nih.gov/genbank/
[1192] https://www.ncbi.nlm.nih.gov/datasets/cgr/
[1193] https://www.ncbi.nlm.nih.gov/refseq/
[1194] https://www.ncbi.nlm.nih.gov/clinvar/

NLM continued its leadership in health data standards by maintaining and expanding several core terminologies used in clinical care, research, and health IT systems, ensuring the precise and current representation of clinical terms and codes.[1195] Between FY22 and FY24, NLM supported the expansion of the International Edition of Systematized Nomenclature of Medicine – Clinical Terms, contributing nearly 25,000 concepts to the International Edition and more than 1,700 concepts to the U.S. Edition to enable users to capture information specific to the U.S. health care system. In the same period, NLM also added over 6,000 new terms to Logical Observation Identifiers Names and Codes, which facilitates consistent representation of laboratory information. NLM also expanded RxNorm, which provides normalized names for generic and branded drugs, by adding more than 550 new medication terms. In FY24, NLM released an updated application programming interface to streamline automated access to these terminologies, supporting interoperability across healthcare and research platforms.

The Alliance of Genome Resources integrates six major model organism databases, including those for yeast, zebrafish, and fruit flies, into a unified platform.[1196] Led by NHGRI, with co-funding from NHLBI and ODSS, this open-access resource enables cross-species comparisons and gene function analysis. By reducing access barriers, the Alliance empowers both large and small research institutions to engage in genomic discovery and facilitates translational insights by linking model organism findings to human health.

The NHLBI's Trans-Omics for Precision Medicine (TOPMed) program integrates whole genome sequencing and multi-omics data, such as metabolomics, epigenomics, and transcriptomics, with a wide array of molecular, clinical, behavioral, and environmental datasets from population-based studies.[1197] This expansive dataset is hosted on a cloud-based ecosystem that enables researchers to securely access, analyze, and build upon TOPMed data using customizable workflows and tools. In 2024, NHLBI launched the TOPMed AI Coordinating Center to accelerate the use of SI approaches in extracting insights from these datasets. The Coordinating Center also supports scientific collaborations and ensures the harmonization of SI tools used across different research teams working within the TOPMed framework.

The *Research Methods Resources* website, developed by ODP, provides investigators with comprehensive guidance for the design and analysis of prevention research studies.[1198] The platform supports both randomized and non-randomized trials and is especially useful for studies involving group- or cluster-randomized designs. It includes educational materials, detailed methodological explanations, a curated reference library, and a sample size calculator tailored for complex trial designs. The resource is designed to help investigators apply best practices in statistical design and analysis across a variety of biomedical contexts. It also helps promote and strengthen scientific rigor and reproducibility.

To support intramural researchers conducting FDA-regulated studies, the NIH Clinical Center continues to support the *Regulatory Toolbox* website.[1199] The working group leading this effort was established in 2019

[1195] https://www.nlm.nih.gov/oet/ed/healthdatastandards/01-400.html
[1196] https://www.genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/The-Alliance
[1197] https://topmed.nhlbi.nih.gov/
[1198] https://researchmethodsresources.nih.gov/
[1199] https://www.cc.nih.gov/orcs

as an NIH-wide collaboration to provide regulatory information and guidance to the FDA regulated community within the NIH Intramural Research Program. Members include regulatory professionals representing 13 NIH ICs. This centralized resource provides guidance for research involving drugs, biologics, and medical devices, helping investigators navigate regulatory requirements more efficiently. The site offers templates, checklists, and links to relevant policies and regulations.

Knowledge graphs are a structured way to represent complex information as a network of interconnected entities, capturing their relationships and attributes, and they are being increasingly used in biomedical research. NIEHS supported researchers developed the Extracting, Exploring, and Embedding Pathways Leading to Actionable Research platform, a user-friendly interface for exploring biomedical knowledge graphs.[1200] These graphs combine varied data types and visually represent relationships among study variables, enabling researchers to design targeted queries and identify patterns across datasets. The tool supports hypothesis generation and integrative analysis in complex biomedical domains.

The *All of Us* Research Program has become one of the most accessible and participant-rich health research platforms in the U.S. By the end of FY24, the program enrolled over 838,000 participants from across all U.S. states and territories and collected more than 590,000 biosamples. This massive cohort supports research on a wide array of health conditions, enabling scientists to explore a large variety of genetic, environmental, and lifestyle factors. With its focus on scale and participation by everyone, *All of Us* is reshaping the landscape of precision medicine by creating a resource that reflects the U.S. population. *All of Us* also surpassed its goal of engaging 10,000 registered researchers, achieving this milestone more than a year ahead of schedule. More than 13,000 researchers from 920 institutions were actively using the secure, cloud-based Researcher Workbench, which houses over 4,000 terabytes of data by the end of FY24. The platform is open to users across a range of backgrounds, including students, citizen scientists, and academic investigators. This expanded access has catalyzed thousands of research projects and hundreds of publications, demonstrating the *All of Us* role in democratizing access to biomedical data and accelerating discovery in precision medicine.

Building on this rapid expansion of participation and researcher engagement, the *All of Us* Research Program continued to scale its data infrastructure and enhance the usability of its research platform. By the end of FY24, the platform housed a vast array of multimodal data types, including survey responses from 413,000 participants, over 337,000 physical measurements, more than 312,000 genomic sequences, and electronic health records from 287,000 participants.[1201] With over 660 publications already citing *All of Us* data by the end of FY24, the Workbench has proven instrumental in supporting large-scale, population-based research. The continuous addition of new data types and improvements in functionality ensure that researchers have access to increasingly rich and varied datasets for their research.

In parallel, the *All of Us* Research Program released one of the largest and most accessible whole genome sequencing datasets available to researchers, fueling novel discoveries across the fields of genomics, and accelerating discoveries in health and disease. With major genomic data releases in 2022 and 2023,

[1200] Beasley JT, et al. Bioinformatics. 2024 Jan 2;40(1):btad779. PMID: 38175789.
[1201] https://allofus.nih.gov/article/announcement-all-us-research-program-makes-nearly-250000-whole-genome-sequences-available-advance-precision-medicine

researchers had access to 245,000 whole genome sequences and 1,000 long-read sequences, which led to the identification of 275 million previously unreported genetic variants. These data provide an unprecedented opportunity to study human genetic variation at scale and were instrumental in key contributions to genomic science, accelerating discovery and enabling precision medicine.[1202]

In October 2023, the *All of Us* Research Program launched the Center for Linkages and Acquisition of Data to enhance data integration across varied sources.[1203] The Center's mission is to supplement participant-provided data with new types of information, without requiring additional input from participants. By connecting previously siloed data streams, the center helps researchers better understand the social, environmental, and biological drivers of health and disease.

As part of the *All of Us* Research Program, NIEHS is leading efforts to incorporate environmental exposure data into the program's scientific roadmap. This work involves collecting participant addresses, linking them with geospatial models of environmental exposures, and integrating these estimates with biomonitoring data derived from participant blood samples. The goal is to better understand how environmental factors contribute to health outcomes by connecting location-based exposures with biological measurements. This initiative expands the scientific utility of *All of Us* by enabling analyses that reflect real-world environmental influences on disease and wellness.

In 2023, OAR launched the NIH OAR Data Hub, a publicly accessible analytics platform that increases transparency into NIH's HIV research portfolio.[1204] The Hub features interactive dashboards that provide budgetary and scientific details about NIH-funded HIV research, allowing users to explore the landscape of projects by topic area, funding source, or scientific focus. In 2024, OAR added new topical dashboards that enable deeper portfolio analysis of emerging or high-priority research areas. The Hub supports investigators, policymakers, and advocates by offering a centralized, user-friendly tool for understanding NIH's investments in HIV research.

The Dietary Supplement Ingredient Database (DSID), maintained by ODS, provides nationally representative estimates of ingredient levels in dietary supplements sold in the U.S.[1205] Unlike product labels, which may contain imprecise values, DSID estimates are based on chemical analysis of products sampled from the marketplace. The fourth release includes updated ingredient content estimates for adult, children, and prenatal multivitamin/mineral products, as well as omega-3 fatty acid supplements. The DSID supports researchers conducting population-level nutrient intake studies and is designed for research purposes rather than individual product verification. Also developed by ODS, the Dietary Supplement Label Database (DSLD) catalogs label information from dietary supplement products marketed in the U.S., including images of Supplement Facts labels and other printed content.[1206] In FY24, the DSLD grew to include over 190,000 labels, sourced from national survey-reported products and voluntary manufacturer submissions. It supports multiple user groups, including healthcare providers

[1202] Kozlowski E, et al. Am J Hum Genet. 2024 Sep 5;111(9):1797. PMID: 39241755.
[1203] https://allofus.nih.gov/article/announcement-all-us-research-program-establishes-new-center-linkage-and-acquisition-data
[1204] https://oar.nih.gov/nih-hiv-research-program/data-hub
[1205] https://dsid.od.nih.gov/
[1206] https://ods.od.nih.gov/Research/Dietary_Supplement_Label_Database.aspx

seeking information about the supplements used by patients, researchers examining ingredient content, and consumers exploring product details. The DSLD is regularly updated and serves as a vital tool for transparency in the dietary supplement marketplace.

ODS also manages the Computer Access to Research on Dietary Supplements Database, which provides a searchable archive of federally funded research projects related to dietary supplements.[1207] The database includes information on NIH-funded projects dating back to FY99, when dietary supplement research reporting was first standardized across NIH. It also includes partial records from other federal agencies such as the Department of Agriculture and the Department of Defense. The database supports coordination across agencies and facilitates transparency in public investments in dietary supplement research.

Given the central role of repositories in data sharing and reuse, NIAID has invested in an ecosystem of platforms for sharing and analyzing immunological data. ImmPort, a premier public repository for immunological data, serves as a cornerstone resource for storing, managing, and sharing high value clinical and mechanistic immunology datasets.[1208] In addition to offering SI-ready datasets to the research community, ImmPort also serves as the foundational platform for advanced data services offered by resources such as the Immune Tolerance Network's TrialShare, the Human Immunology Project Consortium's ImmuneSpace, the Consortium for Food Allergy Research's FoodSpace, and the Children's Allergy and Asthma Data Repository.

Data sharing and reuse are crucial in research because they enhance transparency, efficiency, and collaboration, ultimately accelerating scientific discovery and benefiting society. Led by NIEHS, the Environmental Health Language Collaborative is an initiative to apply harmonized language standards to environmental health data.[1209] By promoting consistent terminology, the collaborative enhances the classification, interoperability, sharing, and reuse of datasets. This approach helps integrate a variety of data sources, improving their utility for discovery and enabling more rigorous environmental health research. The Data Management Center of Excellence, supported by ODSS, promotes the adoption of best practices for data management and sharing across NIH and the broader research community. The center collects and curates guidance, resources, and tools that support the implementation of FAIR data practices.[1210] It also coordinates with related NIH initiatives to ensure alignment and reduce duplication of effort.

ODSS established a DataCite Consortium membership for NIH to expand access to persistent identifier services for NIH-funded data repositories and knowledgebases.[1211] DataCite is an international nonprofit organization, and through this partnership, repositories can assign Digital Object Identifiers, supporting improved data citation, discoverability, reuse, and long-term access. The consortium model facilitates consistent implementation of data citation standards across the NIH ecosystem. ODSS also supports the

[1207] https://ods.od.nih.gov/Research/CARDS_Database.aspx
[1208] https://immport.org/shared/home
[1209] https://www.niehs.nih.gov/research/programs/ehlc
[1210] https://datascience.nih.gov/data-ecosystem/data-management-center-of-excellence
[1211] https://datascience.nih.gov/datacite-consortium

DataWorks Challenge, a partnership with the Federation of American Societies for Experimental Biology, to highlight the impact of data sharing and reuse on scientific discovery.[1212] The challenge recognizes research teams that demonstrate exemplary data management and sharing practices, and it promotes the value of open science across the biomedical research community. As part of its support for generalist data repositories, ODSS launched the *Generalist Repository Ecosystem Initiative* webinar series.[1213] These webinars connect data repository providers with the research community to share best practices and available resources for sharing NIH-funded research data. The series also promotes coordination and collaboration across data platforms.

Led by ODSS, NIH has made substantial investments in cloud-based infrastructure to support scalable, cross-platform research. The Researcher Auth Service is a cloud-based authentication and authorization system that enables secure, seamless access to NIH-supported data repositories.[1214] The service allows users to log in once and access multiple integrated platforms without needing separate credentials for each. This system simplifies data access and enhances interoperability across NIH's digital infrastructure. The NIH Cloud Platform Interoperability Program aims to create a federated data ecosystem that allows researchers to analyze data across multiple cloud-based repositories. Launched to address data silos among large NIH-funded datasets, the program established shared technical standards, data access models, and authentication processes. An Administrative Coordinating Center was established in FY22 to provide technical, administrative, and project management support across participating platforms.

Also led by ODSS, the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative allows NIH and NIH-funded institutions to create a robust, interconnected data ecosystem that breaks down silos related to generating, analyzing, and sharing research data. STRIDES uses cloud computing, provided by partnerships with commercial cloud providers, to streamline NIH data use.[1215] STRIDES offers customized trainings and promotes best practices designed to help researchers achieve optimal use of cloud-based research technologies. STRIDES is helping accelerate innovation in areas like genomics, imaging, and SI.

To increase cloud adoption across the entire research community, ODSS also launched two companion programs: the High-Value Datasets Program for intramural researchers and contracts, and Cloud Notices of Special Interest for extramural researchers.[1216] These programs support cloud-based analysis, storage, security, and collaboration by leveraging the STRIDES Initiative and partnerships with providers like Amazon Web Services, Microsoft Azure, and Google Cloud. The programs aim to expand access to advanced computing resources and support NIH's broader data science strategy to enhance computational capabilities, data interoperability, and research efficiency.

[1212] https://datascience.nih.gov/dataworks
[1213] https://datascience.nih.gov/grei-webinars-events
[1214] https://datascience.nih.gov/researcher-auth-service-initiative
[1215] https://cloud.nih.gov/
[1216] https://datascience.nih.gov/data-infrastructure/exploratory-cloud-research-program

The NHGRI Genomic Data Science Analysis, Visualization, and Informatics Lab-space provides a secure, cloud-based ecosystem for sharing and analyzing large-scale genomic data.[1217] With over 4.5 petabytes of data representing more than 600,000 participants, the platform democratizes access to genomics research by offering cloud credits to external investigators, including those without prior infrastructure. The platform supports projects from major NIH consortia such as The Genotype-Tissue Expression project, Genomics Research to Elucidate the Genetics of Rare Diseases consortium, and the Telomere-to-Telomere initiative. During its second phase, the platform enhanced user experience and compliance by launching the Data Use Oversight System, which simplifies data access while ensuring adherence to participant consent policies.

Networks and Consortia

NIH supports and fosters collaborative networks and consortia to catalyze scientific progress within and across disciplines. By lowering barriers to sharing, analysis, and validation, they speed the development of new technologies and therapies. The Biomaterials Network, created by NIBIB, is designed to accelerate the development and early dissemination of innovative biomaterials technologies.[1218] This initiative supports the translation of biomaterials from discovery through development to commercialization and clinical use. The network consists of connected resources and platforms that enable researchers to advance materials designed for diagnostics, drug delivery, tissue engineering, and regenerative medicine. By providing a framework for collaboration and knowledge exchange, the Biomaterials Network plays a critical role in fostering innovation and reducing the time from concept to clinic.

In 2022, the NHGRI-led Telomere-to-Telomere Consortium achieved the first complete, gapless sequence of a human genome, significantly advancing our understanding of chromosome structure and function.[1219] The full sequencing builds upon the work of the Human Genome Project, which mapped about 92 percent of the genome in the early 2000s. The last 8 percent proved more challenging because of its highly repetitive nature, especially in the telomeric regions, which protect the terminal regions of DNA from progressive degradation. This comprehensive genome reference improved mapping accuracy for five chromosome arms and enabled the identification of over 2 million additional genomic variants, including those affecting 622 medically relevant genes. This helps answer basic biology questions about how chromosomes properly segregate and divide.

The Human Pangenome Reference Consortium, funded by NHGRI, has released a high-quality collection of human genome reference sequences that captures genetic variation across a wide array of ancestral populations spanning the globe.[1220,1221] This “pangenome” includes sequences from 47 individuals and represents a major advancement over previous human genome references.[1222] For example, the original

[1217] https://www.genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/Genomic-Analysis-Visualization-Informatics-Lab-space-AnVIL
[1218] https://grants.nih.gov/grants/guide/rfa-files/RFA-EB-23-002.html
[1219] https://www.genome.gov/news/news-release/researchers-generate-the-first-complete-gapless-sequence-of-a-human-genome
[1220] Hickey G, et al. Nat Biotechnol. 2024 Apr;42(4):663-673. PMID: 37165083.
[1221] https://www.genome.gov/about-genomics/new-human-pangenome-reference
[1222] Liao WW, et al. Nature. 2023 May;617(7960):312-324. PMID: 37165242.

reference consists of genomes from only about 20 people, with most of the reference sequence from only one person. In FY24, the Consortium funded four new informatics tools awards to facilitate uptake and scientific use of the pangenome reference and ensure its integration into the broader research community. In the future, researchers hope to increase the number of people included in the human pangenome reference to 350, dramatically increasing its potential to advance genetics and lead to new discoveries.

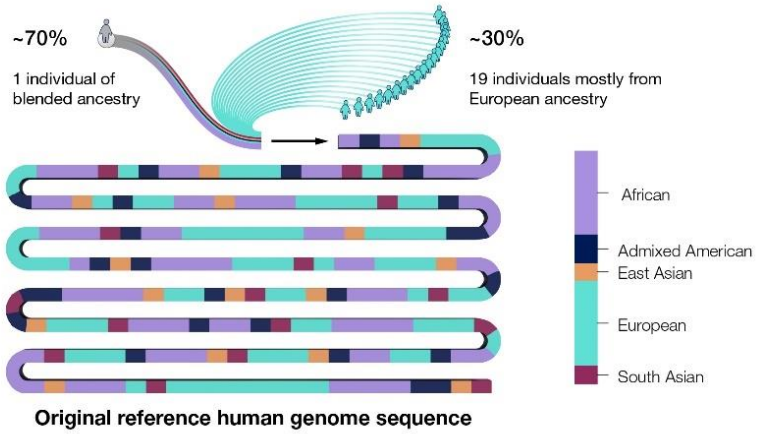


Figure 50. Around 70 percent of the reference human genome sequence came from one person of blended ancestry. The remaining 30 percent came from 19 individuals of mostly European ancestry. Credit: Darryl Leja, NHGRI/NIH

The Impact of Genomic Variation on Function Consortium, launched by NHGRI, builds on the success of The Encyclopedia of DNA Elements Project by examining how genomic variants influence gene function and phenotypes.[1223] Through 26 funded grants, researchers use high-throughput experimental and computational methods to study variant effects across the genome. A central goal is to create an interactive, publicly accessible catalog of variant function, enabling researchers to explore the biological relevance of human genetic variation. The consortium also supports the development of common protocols and standards to ensure that resulting data can be reused across the scientific community.

Now in its fourth phase, The Electronic Medical Records and Genomic Network connects biorepositories and electronic medical record systems to advance genomic discovery and clinical translation.[1224] Funded by NHGRI, the network focuses on integrating complex data such as polygenic risk scores—numerical estimates that summarize an individual's genetic predisposition to diseases—into clinical care, while also addressing ethical, legal, and social implications of genomic research. The current phase includes the Genomic Risk Assessment and Management Network, which is developing tools and protocols to incorporate genomic risk into routine clinical workflows and improve personalized care strategies.

[1223] https://www.genome.gov/Funded-Programs-Projects/Impact-of-Genomic-Variation-on-Function-Consortium
[1224] https://www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE

The Multi-Omics for Health and Disease Consortium, launched by NHGRI in FY23, seeks to advance the application of integrated multi-omic technologies for studying human health and disease.[1225] The primary goal is to develop scalable and generalizable strategies for multi-omics research that can be adopted across a range of biomedical studies.[1226,1227,1228,1229] While the initiative is expected to yield disease-specific insights, its broader value lies in building methods and frameworks that accelerate the use of multi-omics in clinical research. This consortium-based model promotes collaboration among institutions and enhances infrastructure for the generation and interpretation of large, multimodal datasets.

The Genomics-Enabled Learning Health System Network, launched in 2024 and led by NHGRI with co-funding from NCI, NIEHS, and NICHD, seeks to increase the adoption of genomics in clinical care where evidence for utility already exists.[1230] The program focuses on developing, validating, and disseminating tools and resources that help integrate genomics into real-world healthcare settings. It supports more systematic evaluation of how genomic information can improve diagnosis, treatment, and health system performance. By generating implementation evidence and encouraging resource sharing, the network aims to scale the use of genomics across health systems.

The Common Fund's Harnessing Data Science for Health Discovery and Innovation in Africa program, co-led by FIC, NIMH, NIBIB, and NLM, has established a continent-spanning research consortium across 22 African countries and 19 U.S. states.[1231] The initiative supports a data science platform and coordinating center, seven research hubs, seven training programs, four projects on ethical, legal, and social implications, and six research education programs. It also funds 13 discrete data science research projects, creating an ecosystem of partnerships that includes health ministries, academic institutions, non-governmental organizations, and private-sector collaborators. The program will also benefit Americans by fostering innovative data science solutions that can be applied to improve health outcomes in rural and underserved U.S. populations and advancing research collaboration and expertise, potentially leading to breakthroughs that can be applied to similar public health challenges in the U.S.

The Molecular Phenotypes of Null Alleles in Cells program, part of the NHGRI Strategic Vision, seeks to catalog the molecular and cellular consequences of gene knockouts in human cells.[1232] In its initial five-year phase, the program is targeting 1,000 protein-coding genes using optimized *in vitro* multicellular systems to generate null alleles and assess phenotypic outcomes. The program will also establish standard data formats and use cases, and 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 will provide wide-ranging insights into their biological function. This data

[1225] https://www.genome.gov/research-funding/Funded-Programs-Projects/Multi-Omics-for-Health-and-Disease
[1226] Goodrich JA, et al. Environ Int. 2024 Aug;190:108930. PMID: 39128376.
[1227] Wang J, et al. Nat Commun. 2023 Nov 14;14(1):7367.. PMID: 37963892.
[1228] Elliott MD, et al. J Clin Invest. 2024 Sep 3;134(17):e178573. PMID: 39225089.
[1229] Beenken A, et al. J Am Soc Nephrol. 2024 Jul 1;35(7):835-837. PMID: 38819933.
[1230] https://www.genome.gov/Funded-Programs-Projects/Genomics-enabled-Learning-Health-Systems
[1231] https://www.fic.nih.gov/Programs/Pages/harnessing-data-science-for-health-discovery-innovation-africa.aspx
[1232] https://www.genome.gov/research-funding/Funded-Programs-Projects/Molecular-Phenotypes-of-Null-Alleles-in-Cells

will provide a foundation for a better understanding of the mechanisms of action of genes and will help elucidate the roles and relationships of genes and regulatory elements in pathways and networks.

The Institutional Development Award (IDeA) Clinical and Translational Research Network (CTR) Program, led by NIGMS, builds statewide research networks to strengthen clinical and translational research capacity in IDeA-eligible states.[1233] The program was recently divided into two award mechanisms—P50 CTR-N (Network) and P20 CTR-D (Development) awards. The CTR-N supports multi-institutional networks that connect research-intensive institutions with those that have historically had limited NIH funding, often serving medically underserved populations such as those in rural areas.[1234] CTR-N awardees collaborate with Practice-Based Research Networks (PBRNs) to engage primary care practices and community clinics in research. In FY24, NIGMS released a new funding opportunity for CTR-N and supported the first national PBRN summit, which facilitated knowledge sharing to increase participation in clinical studies and establish a strong foundation for a national CTR PBRN organization. The CTR-D aims to expand the CTR program by helping additional institutions build foundational clinical and translational research infrastructure, preparing them to participate more fully in statewide or multi-institutional research networks.[1235] In FY24, NIGMS funded four new CTR-D awards and released a new funding opportunity to continue this expansion.

The IDeA States Pediatric Clinical Trials Network builds pediatric clinical research capacity in IDeA program states, with a focus on reaching populations that may not otherwise have access to state-of-the-art pediatric trials.[1236] The network, led by ECHO, is a collaborative initiative involving multiple NIH ICOs, including the NIGMS and NICHD. The network engages institutions in infrastructure building and provides training and tools to increase readiness for pediatric clinical research in underserved areas.

Policies, Programs, and Processes that Enable Research

NIH's policies, programs, and processes are the backbone of a strong, trustworthy, and adaptive research system. By continuously assessing, updating, and harmonizing practices—from how research studies are reviewed and funded to how data and tools are shared—NIH positions itself to tackle complex problems ahead. NIH has undertaken multiple efforts to strengthen the integrity of its peer review process, ensuring it remains transparent, unbiased, and trustworthy.[1237]

Beginning in January 2025, NIH implemented a simplified peer review framework for most research project grants. The Simplified Framework for NIH Peer Review Criteria retains the five regulatory criteria (Significance, Investigators, Innovation, Approach, Environment) but reorganizes them into three factors. The reframing of the criteria serves to focus reviewers on three central questions reviewers should be evaluating: How important is the proposed research, how rigorous and feasible are the methods, and whether the investigators and institution have the expertise/resources necessary to carry out the project. The aim of this simplification is to promote a more balanced and fairer review process that highlights the

[1233] https://nigms.nih.gov/Research/DRCB/IDeA/Pages/default
[1234] https://grants.nih.gov/grants/guide/pa-files/PAR-23-241.html
[1235] https://grants.nih.gov/grants/guide/pa-files/PAR-23-257.html
[1236] https://echochildren.org/idea-states-pediatric-clinical-trials-network/about-ispctn/
[1237] https://grants.nih.gov/policy-and-compliance/policy-topics/peer-review/simplifying-review

scientific and technical merit of proposals. This change is intended to help identify the most innovative and promising science and reduce the influence of reputational bias.[1238] By narrowing the review scope to core evaluative criteria, the new framework supports a more focused peer review process. It also reduces reviewer burden by shifting policy compliance activities to NIH staff.

CSR is leveraging SI tools to detect potential reviewer collusion, supporting efforts to safeguard the integrity of NIH's peer review process.[1239] These tools are complemented by the establishment of a dedicated Review Integrity Officer and the promotion of accessible reporting mechanisms. In 2024, CSR implemented mandatory review integrity training for all NIH reviewers, focused on identifying and addressing breaches of conduct. Over 90 percent of reviewers surveyed after the training reported increased confidence in both recognizing integrity issues and contacting NIH with concerns. These measures reinforce the agency's commitment to ensuring fairness, accountability, and public trust in the peer review process.

To strengthen the breadth of the NIH reviewer pool, CSR has expanded recruitment through multiple mechanisms, including the Early Career Reviewer program, targeted outreach to mid-career scientists, and internal tools to identify subject-matter experts.[1240] These efforts support broader geographic, institutional, and career-stage representation on peer review study sections. NIH also implemented a "reasonable service" policy to prevent overuse of highly active reviewers and to reduce undue influence by any one individual.

Lastly, The Evaluating Panel Quality in Review process, developed by CSR, systematically reviews the scope and structure of NIH peer review panels to ensure alignment with emerging scientific trends.[1241] Since its launch in 2019, the process has reviewed or is actively evaluating 151 peer review study sections, often leading to the sunsetting of outdated panels and the creation of new ones. For example, recent evaluations incorporated fast-growing areas such as cancer immunotherapies and mobile health technologies into newly structured review groups. CSR aims to review every standing study section at least once every five years, ensuring that NIH peer review evolves alongside biomedical science.

In 2023, NIH implemented a new *Data Management and Sharing Policy* requiring researchers to submit and follow a Data Management and Sharing Plan for all NIH-funded or conducted research that generates scientific data. This policy promotes open science and responsible stewardship of public resources, while allowing justified limitations on data sharing when appropriate. NIH is implementing a new streamlined Data Management and Sharing Plan template format to reduce administrative burden and aid policy compliance monitoring.

Launched in 2024, the NIH Replication to Enhance Research Impact Initiative is a pilot program to test whether direct replication of NIH-funded studies can improve the reproducibility of biomedical research.[1242] Through partnerships with contract research organizations, NIH will replicate selected studies

[1238] https://grants.nih.gov/policy-and-compliance/policy-topics/peer-review/simplifying-review/framework
[1239] https://public.csr.nih.gov/RevPanelsAndDates/MeetingOverview/IntegrityInReview
[1240] https://public.csr.nih.gov/ForReviewers/BecomeAReviewer/ECR
[1241] https://public.csr.nih.gov/EvaluationInitiatives/CSREnquire
[1242] https://commonfund.nih.gov/replication-initiative

and evaluate the conditions that support or hinder successful replication. Findings from the pilot, expected in 2026, will inform future policies on enhancing rigor and transparency in research.

ODP systemically conducts portfolio analyses and impact assessments of NIH-funded prevention research to evaluate alignment with public health needs and scientific priorities.[1243] Using a comprehensive taxonomy, ODP categorizes NIH prevention projects based on leading causes of death, risk factors, population demographics, study design, and type of prevention (primary or secondary). These analyses help identify research gaps, guide future funding strategies, and ensure investments are targeted to areas with the greatest potential public health benefit. Recent publications from this effort have addressed healthcare delivery, opioid research, and tobacco research, among others.[1244,1245,1246]

The NIH Sustainable Software Program Initiative, launched in 2024, enhances the longevity and impact of biomedical research software tools by encouraging best practices in software engineering and open science.[1247] Led by ODSS, the program includes a career development component for Research Software Engineers, acknowledging their key role in the scientific workforce. Through administrative supplements and infrastructure support, the initiative promotes greater usability, quality, and community engagement in NIH-funded software development.

The *Blueprint for the Use of Social and Behavioral Science to Advance Evidence-Based Policymaking*, published in 2024, provides a high-level strategy for integrating social and behavioral science into federal governance.[1248] Developed through the White House Office of Science and Technology Policy and supported by OBSSR, the blueprint outlines actionable steps for applying behavioral and social sciences across policy domains. It emphasizes a systems-level understanding of behavior, spanning individuals to institutions, and encourages federal agencies to embed social science expertise into their operational frameworks. The document serves as both a policy guide and a call to expand investment in evidence-informed interventions.

Another report from the National Academies, co-sponsored by OBSSR and other NIH ICs, explores the influence of behavioral economics on public policy across six policy domains: health, retirement benefits, climate, the social safety net, education, and criminal justice.[1249] The report concludes that behavioral economics principles are indispensable to policy design and calls for the integration of behavioral scientists into policymaking processes. It also identifies gaps in the existing evidence base and outlines a research agenda to improve methodology and expand applications.

[1243] https://prevention.nih.gov/funding/portfolio-analysis-nih-prevention-research
[1244] Ganoza LF, et al. Med Care. 2023 Feb 1;61(2):75-80. Epub 2022 Dec 6. PMID: 36630558.
[1245] Klabunde CN, et al. Prev Sci. 2023 Aug;24(6):1091-1101. Epub 2023 Jul 15. PMID: 37452891.
[1246] Sharma K, et al. Nicotine Tob Res. 2023 May 22;25(6):1082-1089. PMID: 36789895.
[1247] https://datascience.nih.gov/tools-and-analytics/administrative-supplements-to-support-enhancement-of-software-tools-for-open-science
[1248] https://bidenwhitehouse.archives.gov/wp-content/uploads/2024/05/Blueprint-for-the-Use-of-Social-and-Behavioral-Science-to-Advance-Evidence-Based-Policymaking.pdf
[1249] https://nap.nationalacademies.org/catalog/26874/behavioral-economics-policy-impact-and-future-directions

In 2024, an OBSSR-supported study evaluated the impact of NIH's 2015 guidance on funding priorities for health economics research.[1250,1251] Using a machine learning approach combined with expert input, the analysis tracked submission and funding trends for health economics applications before and after the guidance was released. Results showed that although application and funding rates had been declining prior to 2015, both increased following the issuance of the guidance. The study demonstrates how formal policy statements can shape research activity and promote investment in fields of interest to NIH.

The *All of Us* Research Program Advisory Panel released a strategic report in 2024 that outlines the program's next phase and long-term vision. Informed by input from a working group of advisors, the report evaluates past achievements, identifies areas for improvement, and recommends strategies to expand scientific impact and operational sustainability. The roadmap addresses key program components such as participant engagement, data usability, and platform development. It is intended to guide future decision-making and ensure the program remains at the forefront of precision medicine research.

To strengthen researcher engagement and accelerate the scientific use of its data, the *All of Us* Research Program established the Extramural Program to Advance Research. Phase 1 awarded 25 one-year administrative supplements across 13 NIH ICOs, while Phase 2 issued two new funding announcements for external grants. Nearly $220 million in research and training awards were distributed from FY22 to FY24 to support work leveraging *All of Us* data.[1252] The program also established a network of investigators to share tools, insights, and best practices, thereby building a collaborative research community focused on data-driven team science.

A 2024 report from NCATS highlights both the opportunities and challenges associated with decentralized clinical trials, which are designed to broaden research participation, particularly among individuals in rural or underserved areas.[1253,1254] These trials allow for remote participation, potentially increasing inclusivity and efficiency in clinical research. The report, developed with extensive community input, provides recommendations for expanding the use of decentralized trials, including guidance on overcoming logistical, regulatory, and technological barriers. As decentralized trial designs become more common, the report serves as a roadmap to optimize implementation.

The NCATS Streamlined, Multisite, Accelerated Resources for Trials Institutional Review Board (IRB) Reliance Agreement reached a major milestone in 2022, with more than 1,000 participating institutions.[1255] This initiative provides a master IRB agreement that allows a single IRB to oversee multisite studies, replacing the need for separate reviews at each participating site. By enabling institutions to rely on a central IRB and facilitating agreement through an easy-to-use platform, the agreement significantly

[1250] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-025.html
[1251] Burgdorf CE, et al. PLoS One. 2024 Feb 14;19(2):e0284235. PMID: 38354126.
[1252] https://allofus.nih.gov/article/announcement-nih-awards-97-million-advance-use-all-us-research-program-dataset
[1253] https://ncats.nih.gov/news-events/news/ncats-report-highlights-decentralized-clinical-trials-challenges-opportunities
[1254] https://ncats.nih.gov/sites/default/files/2024-06/RFI-DCT-Report-for-public-website-FINAL-508.pdf
[1255] https://ncats.nih.gov/news-events/news/nationwide-IRB-reliance-agreement-aimed-at-speeding-research-reaches-1000-signatories

reduces the time required to initiate multisite research from months to weeks. It maintains strong protections for research participants while improving efficiency and coordination in clinical trial startup.

The NIH Clinical Center established internal mechanisms to strengthen regulatory and operational support for clinical research conducted across the NIH Intramural Research Program. The Stability Testing Advisory Committee offers specialized guidance to investigators and sponsors on how to conduct stability testing for investigational products, ensuring compliance with quality assurance standards and regulatory expectations. The Protocol Navigator Working Group facilitates cross-Institute coordination around clinical protocol development and implementation. This working group serves as a hub for sharing updates on clinical research policy, regulatory guidance, and operational best practices. Together, these structures improve protocol quality, ensure regulatory compliance, and streamline processes across NIH's clinical research portfolio. Lastly, the NIH Clinical Center developed an Environmental Monitoring Dashboard for use in manufacturing and compounding facilities. The tool enables real-time visualization of environmental data, supports the creation of cleaning schedules, and generates trend and tracking reports.

The NIH Clinical Center also implemented a unified, 24/7 model of care for pediatric inpatients enrolled in clinical research studies, spanning 15 NIH ICs. Under this system, pediatric-trained hospitalist physicians provide round-the-clock care and collaborate directly with research teams to ensure high-quality, age-appropriate treatment for children ages 2 to 18. The model also integrates Child Life services to offer emotional support to pediatric participants and their families during medical procedures. This cross-Institute approach strengthens clinical care consistency and improves the patient experience for children participating in NIH research.

Research Models

Scientists often carry out basic research in "model systems," which are easier to work with and exist in precisely defined, controlled settings. NIH funds the development of and infrastructure supporting a wide range of research models, ranging from the tiny soli nematode *C. elegans* to nonhuman primates; and more recently, NAMS—such as computational, biochemical, or cell-based model systems—that can replicate aspects of human biology and provide a complementary approach to traditional model systems.

ORIP supports a national network of nonhuman primate research resources that underpin critical discoveries in neuroscience, aging, infectious disease, regenerative medicine, and more. These resources include the National Primate Research Centers,[1256] the Caribbean Primate Research Center, and colonies of specific pathogen-free macaques and baboons, as well as specialized vervet and squirrel monkey resources.[1257] ORIP's investments have enabled genomic sequencing of nonhuman primates and the discovery of numerous animal models for human diseases, which are shared with the research community via a National Primate Research Centers-supported database.[1258] To further strengthen this infrastructure, the Research Centers recently established a coordinating center for aging research that aggregates data on physiological and pathological changes across the lifespan. Collectively, these resources provide

[1256] https://www.nprcresearch.org/research/page/National_Primate_Research_Centers
[1257] https://orip.nih.gov/division-comparative-medicine/research-resources-directory
[1258] https://mgap.ohsu.edu/

essential platforms for modeling disease mechanisms, evaluating interventions, and translating basic research into clinical advances.

ORIP supports two complementary programs aimed at advancing the quality and translational relevance of research models in biomedical research. The Resources for Improving Rigor and Reproducibility of Animal Models program, launched in 2022, supports projects that validate and characterize animal models to ensure that preclinical findings are more reliably translated to clinical outcomes.[1259] This includes work on Drosophila models of mitochondrial disease and zebrafish models of human conditions. ORIP's Resource-Related Research Program supports the development, refinement, and accessibility of research models and associated materials such as reagents, genetic stocks, and diagnostic tools, for use across the biomedical research community.[1260] These projects span a wide range of species including worms, flies, rodents, and swine. The program also funds the development of new approach methodologies (NAMs)—lab or computer-based research approaches intended to more accurately model human biology and complement traditional research models—such as *in vitro* systems, in silico models, and biocomputing strategies. Together, these initiatives expand the experimental toolkit for translational research and strengthen the rigor of NIH-supported studies.

ORIP also supports the development of animal model-based resources through its participation in Phase 2 of the NIH Common Fund's Somatic Cell Genome Editing program, which is working to improve the efficacy and specificity of gene editing approaches.[1261] Building on the earlier Phase 1 Animal Models Initiative, which produced and validated rodent and pig reporter strains for detecting genome editing outcomes, ORIP launched four testing centers for the development of somatic cell genome editing in model organisms. These centers specialize in major mammalian species, including rodents, pigs, and nonhuman primates, and are designed to accelerate technology development, conduct preclinical testing of genome editing therapeutics, and serve as a resource for the broader biomedical community.[1262] Each center provides access to validated model organisms and genome editing tools while supporting ongoing innovation and rigorous preclinical assessment of new technologies.[1263]

The ORIP-led initiative on environmental extrinsic factors supports systematic studies of how environmental conditions affect animal models in research. This includes funding for advanced instrumentation that can monitor, record, and analyze variables such as temperature, humidity, noise, and light in real time.[1264] The program aims to improve experimental rigor and reproducibility by helping investigators account for environmental influences that may alter biological or behavioral outcomes. Research supported through this initiative is designed to be broadly applicable across ICs and disciplines.

The Animal and Biological Material Resource Centers program, supported by ORIP, ensures the availability for the research community of specialized animal colonies and biological materials, including genetic

[1259] https://grants.nih.gov/grants/guide/pa-files/PAR-23-039.html
[1260] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-013.html
[1261] https://csge.ucdavis.edu/
[1262] https://nstc.missouri.edu/
[1263] https://www.bcm.edu/research/research-centers/baylor-rice-genome-editing-testing-center
[1264] https://www.grants.nih.gov/grants/guide/pa-files/PAR-24-167.html

stocks, reagents, and cell lines.[1265] These centers maintain and distribute high-quality resources nationally while supporting community-driven acquisition, cryopreservation, and genetic validation. Between FY22 and FY24, the program served tens of thousands of NIH-supported investigators and contributed to more than 2,100 peer-reviewed publications. To further strengthen this program, ORIP introduced a Curation and Informatics component at each center to enhance the generation, validation, and preservation of information about animal models, biomaterials, stock usage, user access, and research impact.[1266] These additions improve discoverability and long-term utility, increase the transparency of how resources are used, and enhance the rigor and transparency of biomedical research.

ORIP supports the development of scalable, cost-effective cryopreservation techniques to safeguard the long-term viability of animal models critical to biomedical research.[1267] These efforts have led to innovations such as a robust, easy-to-implement method for cryopreserving fruit fly embryos, as well as technologies and devices that extend cryopreservation to aquatic species.[1268,1269] The program has funded both resource centers and small businesses to broaden the accessibility of germplasm preservation methods across research communities.

The Centers for Precision Disease Modeling Program, supported by ORIP, funded three new centers for the creation and distribution of precision animal models to study the impact of specific human genetic variants.[1270] Each center evaluates the likelihood that a variant causes disease using optimized model organisms such as mice, zebrafish, flies, and human induced pluripotent stem cells. The program emphasizes community-nominated unique human genomic variants to support cost-effective, high-throughput model development. From FY22 through FY24, centers produced more than 250 disease models for use by 91 institutions across a wide range of human conditions, including ciliopathies, neurodevelopmental defects, and connective tissue disorders.

The Caenorhabditis Genetics Center, supported by ORIP, is a globally utilized resource for maintaining and distributing genetically characterized strains of the model organism *C. elegans.*[1271] Established in 1979, the center has expanded to house over 27,000 nematode strains and has distributed more than 30,000 annually since 2022 to researchers in approximately 1,500 laboratories worldwide. These strains have contributed to over 600 NIH-funded projects from 22 NIH ICs and are cited in more than 800 publications each year.[1272,1273,1274] *C. elegans* has enabled numerous insights into genetics, aging, and disease due to its tractability and relevance to human biology. The center plays a critical role in supporting reproducible science through centralized, quality-controlled access to essential model organism stocks.

[1265] https://orip.nih.gov/division-comparative-medicine/research-resources-directory
[1266] https://orip.nih.gov/funding/guidance-applicants/faq-p40-curation-and-informatics-component
[1267] Guo Z, et al. Adv Sci (Weinh). 2024 Jan;11(3):e2303317. PMID: 38018294.
[1268] Bodenstein S, et al. Cryobiology. 2023 Dec;113:104792. PMID: 37944879.
[1269] Hosseini S, et al. Micro Nano Eng. 2024 Sep;24:100277. PMID: 39157761.
[1270] https://www.bcm.edu/research/research-centers/center-for-precision-medicine-models
[1271] https://cgc.umn.edu/
[1272] Yee C, et al. Nat Neurosci. 2024 Sep;27(9):1695-1707. Erratum in: Nat Neurosci. PMID: 39103556.
[1273] Cornell R, et al. Nat Commun. 2024 Aug 3;15(1):6594. PMID: 39097618.
[1274] Gao SM, et al. Nat Aging. 2024 Jul;4(7):998-1013. PMID: 38816550.

Through its support of the NIH Common Fund Complement Animal Research in Experimentation program,[1275] NIEHS is developing a framework for evaluating NAMs that offer human-relevant models for studying health and disease.[1276] The initiative includes a landscape analysis of *in vitro* models, such as organoids (miniaturized and simplified versions of an organ that mimic the key function, structure, and biology), in silico models such as "digital twins" (virtual models of real-world systems), and in chemico systems such as cell-free models that use chemical reactivity methods and biocomputers to screen compounds. It also considers data infrastructure needs, including FAIR data principles and SI-readiness of datasets, used to develop and validate NAMs. These efforts aim to establish scientific confidence in non-animal methods and expand their use in biomedical research.

A person's voice is produced by the vibration of their vocal folds, and injuries or surgeries can lead to voice disorders. Reliable models of human vocal fold tissue were previously unavailable. NIDCD-funded researchers have developed an *in vitro* vocal fold tissue model from adult human cells that were reprogrammed into stem cells.[1277] This model responds to environmental insults, such as cigarette smoke, with an inflammatory reaction similar to that of actual human vocal fold tissue. Ongoing research aims to use these models to better understand injury responses and to develop regenerative treatments for damaged vocal fold tissue.

Training, Workshops, and Capacity Building

Key to NIH's efforts in supporting research resources and infrastructure is enhancing the dissemination of research, promoting collaboration, and supporting training and capacity building efforts in biomedical, behavioral, and social sciences. For example, OBSSR's Director's Webinar Series features leading researchers and emerging voices presenting on a wide array of topics in behavioral and social sciences research.[1278] These webinars serve as a key vehicle for disseminating new findings, raising awareness about priorities, and engaging with the broader scientific and public health communities. All webinars are recorded and archived on OBSSR's website, expanding their reach and utility as an ongoing educational resource.

The NIH Behavioral and Social Sciences Research Festival is an annual event coordinated by OBSSR and the NIH Behavioral and Social Sciences Research Coordinating Committee to showcase innovative, NIH-supported research in the behavioral and social sciences.[1279] The festival brings together NIH staff, funded investigators, and community stakeholders to highlight major advances, emerging topics, and the role of behavioral and social sciences in improving human health for all. By representing the variable research portfolios of NIH ICs, the event facilitates knowledge exchange across disciplines and supports OBSSR's efforts to promote the visibility and impact of behavioral and social sciences. It also informs strategic planning and fosters collaboration within the broader NIH research community.

[1275] https://commonfund.nih.gov/complementarie
[1276] van der Zalm AJ, et al. Arch Toxicol. 2022 Nov;96(11):2865-2879. PMID: 35987941.
[1277] Lungova V. Methods Mol Biol. 2022;2454:365-380. PMID: 33959913.
[1278] https://obssr.od.nih.gov/news-and-events/events/obssr-directors-series-webinars
[1279] https://obssr.od.nih.gov/news-and-events/events/nih-behavioral-and-social-sciences-research-festival

The NIH Matilda White Riley Behavioral and Social Sciences Honors program, administered by OBSSR, celebrates the legacy of Dr. Riley by recognizing exceptional contributions to the behavioral and social sciences.[1280] Established originally as a distinguished scholar lecture, the program expanded in 2016 to include an early-stage investigator paper competition. Each year, OBSSR honors selected early-stage investigators whose research exemplifies scientific excellence and relevance to public health. The program highlights the value of behavioral and social sciences in advancing NIH's mission and helps foster the next generation of behavioral and social scientists.

ODP supports training and dissemination of advanced research methodologies through both live and self-paced online learning formats. The *Methods: Mind the Gap* webinar series focuses on emerging and best practices in research design, measurement, data analysis, and other key methodologies used in prevention science.[1281] These webinars serve as an educational forum for the scientific community and often feature national and international experts in research methodology. Each session includes a presentation, Q&A session, and accompanying materials such as slides, key references, and video recordings, which are made publicly available through the ODP website.

The ODP-led *Prevention in Focus* webinar series highlights the latest findings and innovations in prevention science through talks delivered by leading researchers in the field.[1282] Topics covered included food insecurity, Alzheimer's disease prevention, menthol smoking cessation, health literacy, and multimorbidity measurement, among others. These webinars are open to the public and the broader scientific community and aim to increase awareness of evidence-based prevention strategies and encourage cross-sector dialogue. Recordings, presentation materials, and related resources are made available on the ODP website, promoting continued learning and dissemination of prevention research. ODP also offers an online course titled *Pragmatic and Group-Randomized Trials in Public Health and Medicine*, which helps researchers design and analyze trials involving group or cluster randomization.[1283] The course covers statistical methods, design choices, and practical issues such as contamination and ethical considerations, ensuring that investigators are equipped to conduct rigorous trials in real-world public health settings.

With a focus on strengthening NIH programs, ODP offers expert consultation services on research methodology to NIH ICOs in the areas of study design, analysis plans, and sample size determination. These consultations are often provided during the planning phases of large initiatives, ensuring that studies are methodologically sound from the outset. ODP staff frequently serve on Data Safety and Monitoring Boards, Technical Assistance Working Groups, and Design and Analysis Committees, contributing methodological expertise across NIH programs. Past collaborations include work on the Common Fund's Health Care Systems Collaboratory and NHLBI's Disparities Elimination through Coordinated Interventions initiative, demonstrating ODP's wide-ranging methodological impact.

[1280] https://obssr.od.nih.gov/news-and-events/events/nih-matilda-white-riley-behavioral-and-social-sciences-honors
[1281] https://prevention.nih.gov/education-training/methods-mind-gap
[1282] https://prevention.nih.gov/education-training/prevention-focus-webinars
[1283] https://prevention.nih.gov/education-training/pragmatic-and-group-randomized-trials-public-health-and-medicine

OPA supports the NIH mission by expanding its analytic capabilities through development and dissemination of new methods, computational tools, and best practices. To build capacity for data-informed decision making across NIH, OPA expanded both the usage and visibility of its portfolio analysis tools. In addition to increasing tool adoption, OPA provided a range of training opportunities, consultations, and tutorials tailored to staff across NIH ICOs. These activities helped equip NIH program staff with the skills needed to conduct high-quality portfolio analyses and improve strategic planning.

ODSS has hosted a range of strategic workshops, seminars, and community events to advance data sharing, responsible SI development, and sustainable infrastructure for biomedical research. These efforts reflect NIH's growing investment in transparency, interoperability, and open science practices. ODSS's *Data Sharing and Reuse* seminar series highlights success stories and practical lessons in research data reuse.[1284] Each monthly session features NIH-funded investigators whose work exemplifies the value of open data, with a focus on advancing discovery and maximizing the return on research investments. Presentations are recorded and archived to support ongoing learning across the research community.

Partnerships are essential for advancing efforts to enhance the quality and impact of research initiatives. ODSS partnered with experts from the GO FAIR Foundation to host a workshop focused on the practical implementation of the FAIR Principles in their research workflows.[1285] Participants learned about theoretical foundations and hands-on strategies for improving the discovery, attribution, and reuse of biological and biomedical research data. ODSS also partnered with the Data Curation Network to host the *Supporting Transparent and Interoperable Access to Research Services* workshop. This event brought together institutional repository managers, data curation professionals, and service providers from academic libraries to discuss shared infrastructure needs and opportunities for collaboration.[1286] The event focused on strengthening institutionally based data services and building communities of practice to support high-quality research data sharing and stewardship across institutions.

Workshops and meetings are equally important for fostering collaboration, sharing knowledge, and establishing best practices to advance research. To promote coordination and long-term success among NIH-funded biomedical data platforms, ODSS hosted a meeting consisting of awardees from the Data Repository and Knowledgebase program.[1287] The event enabled funded teams to share progress updates, align their efforts, and define a collective vision for repository infrastructure and services. It also served as an incubator for a community of practice aimed at sustaining a more connected and user-oriented biomedical data ecosystem. ODSS convened the *Transparency for Data and Model Reuse* workshop to address the growing role of SI in biomedical research and the importance of ethical, responsible SI development.[1288] Participants identified key tools and capability gaps related to data and model transparency and discussed preliminary guidelines for researchers funded by NIH to use or develop SI tools

[1284] https://datascience.nih.gov/nih-data-sharing-and-reuse-seminar-series
[1285] https://datascience.nih.gov/getting-practical-with-the-FAIR-principles
[1286] https://datascience.nih.gov/data-curation-network-event-series
[1287] https://datascience.nih.gov/data-ecosystem/biomedical-data-repositories-and-knowledgebases
[1288] https://datascience.nih.gov/artificial-intelligence/initiatives/ethicalframework2024

responsibly. The workshop marked an early step in shaping a shared NIH framework for transparent and reproducible SI practices.

Other Research Resources

NIH is bolstering the national biomedical research ecosystem with modernized shared infrastructure and targeted training, while promoting standardized methods, reference materials, and definitions that expand access, drive collaboration, and strengthen rigor, interoperability, and reproducibility to speed discovery. For example, the National and Regional Resources program, launched by NIGMS in FY19, continues to provide support for a wide range of research infrastructure used by investigators across the country.[1289] These resources include state-of-the-art facilities, advanced instrumentation, reagents, software tools, and services that are accessible on a national, regional, or multi-state scale. The program's design encourages broad user engagement while yielding economies of scale that improve research efficiency. By enhancing access to cutting-edge technologies and services, the program helps ensure that NIH-supported scientists can leverage the tools needed to pursue innovative biomedical research.

The John Lewis NIMHD Research Endowment Program supports research infrastructure and training capacity at eligible colleges and universities through institutional endowments for up to five years.[1290] Revitalized by the *John Lewis NIMHD Research Endowment Revitalization Act of 2021*, the program awarded $60 million in 2023 to six institutions to expand their biomedical research capabilities and support development and expansion of the research capacity and infrastructure.

Through its biomedical and biobehavioral research facilities construction program—which includes modernization to support new technologies—ORIP empowers advanced collaborative research with national impact.[1291] A FY23 construction grant for expanding a 13,000-square-foot cyclotron facility was awarded to the University of Wisconsin-Madison to broadly advance basic, translational and clinical nuclear medicine research and foster research collaborations nationwide. As a cornerstone of nuclear medicine, the Cyclotron Facility will be pivotal to support over three dozen clinical research projects on advancing radiopharmaceutical innovation and medical imaging. Upon completion, the Facility will quadruple the production capacity for radiotracers for CT scans and other advanced medical imaging, speeding new discoveries and advancing treatments for chronic pain and precision cancer therapies as well as improving imaging diagnosis and treatment of many diseases including AD, Parkinson's disease, and others.

The Analytical Methods and Reference Materials Program, led by ODS, develops validated analytical chemistry methods and reference materials to enhance the rigor and reproducibility of research involving dietary supplements, natural products, and nutrient biomarkers.[1292] Between FY22 and FY24, program activities resulted in 13 new reference materials, a new method validation approach, three laboratory

[1289] https://www.nigms.nih.gov/Research/mechanisms/Pages/NIGMS-National-and-Regional-Resources-(R24)
[1290] https://www.nimhd.nih.gov/research/extramural-research/john-lewis-nimhd-research-endowment-program
[1291] https://orip.nih.gov/division-construction-instruments/extramural-construction-programs
[1292] https://ods.od.nih.gov/Research/AMRMProgramWebsite.aspx

quality assurance studies, a searchable reference material database, and 16 publications focused on guidance and methods development.[1293,1294,1295,1296]

Released in 2022, the *Ontologies in the Behavioral Sciences: Accelerating Research and the Spread of Knowledge* report[1297] is a National Academies consensus study sponsored by OBSSR, NCI, NIA, NLM, NSF, and professional associations. The report supports OBSSR's goal of building a cumulative, interoperable knowledge base in behavioral and social sciences research. It highlights how ontologies, structured systems of concepts and relationships, can promote data reuse, enable cross-disciplinary communication, and increase rigor and reproducibility in behavioral and social sciences research. The recommendations emphasize the value of adopting ontology development as a shared community standard and provide a roadmap for implementation. This foundational work strengthens the infrastructure for scalable and integrated behavioral science.

[1293] Camara JE, et al. Anal Bioanal Chem. 2023 Feb;415(5):809-821. PMID: 36507958.
[1294] Fong Sam et al. J AOAC Int. 2024 Nov 1;107(6):1027-1037. PMID: 39067039.
[1295] Wise SA, et al. Anal Bioanal Chem. 2024 Apr;416(9):2335-2358. PMID: 38236394.
[1296] Sempos CT, et al. Anal Bioanal Chem. 2022 Nov;414(27):7793-7803. PMID: 36109397
[1297] https://www.nationalacademies.org/our-work/accelerating-social-and-behavioral-science-through-ontology-development-and-use

Chapter 4: Centers of Excellence

Alzheimer's Disease Research Centers

Establishment of the Alzheimer's Disease Research Centers

There is substantial interest from Congress and the public regarding research that focuses on Alzheimer's disease and related dementias (AD/ADRD), including on the causes, diagnosis, treatment, and prevention of these diseases, as well as on differences in cost and coordination of care between communities. 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, and interest in AD/ADRD that was emerging from the work of NIH grantees and other researchers. Another incentive for these centers was the prospect that an explosion of AD/ADRD cases due to population aging could lead to a medical and social crisis. Although each center has its own emphasis, the ADRC program's principal objective is threefold: to conduct cutting-edge basic, clinical and translational multidisciplinary research; to train the next generation of researchers; and to provide the public, including care providers, with information about research findings, access to support services, and opportunities to participate in research.

Over the 40 years of the program, there has been a major shift from research focused on advanced dementia with a heavy emphasis on genetics to much earlier stages of the disease with a focus on better understanding risk factors and developing and validating specific biomarkers. These changes address the increasing recognition that most older adults have a combination of pathological processes and complex interactions that results in varied clinical presentations and provide evidence to support a precision medicine approach to AD/ADRD.

How the ADRCs Function Within the NIH Framework

NIH currently funds 37 ADRCs and the National Alzheimer's Coordinating Center (NACC),[1298] 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[1299] (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 individuals for comparison. Funding for the ADRCs comes from NIA through the P30 center core grant mechanism. Each ADRC is funded for five years and ADRCs compete through a merit-based peer review process for additional years of funding. New applicants for ADRC funding compete with existing grantees.

[1298] https://naccdata.org/
[1299] https://ncrad.iu.edu/

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,[1300] frontotemporal disorders,[1301] and vascular dementia.[1302] It is common for people to have mixed dementia,[1303] which is a combination of two or more types of dementia. For example, some people have both AD and vascular dementia. Additionally, a new form of dementia was defined in 2018, called Limbic-predominant age-related TDP-43 encephalopathy (LATE).[1304] LATE is very similar to AD in its symptoms but usually has a slower onset and occurs (and is quite common) later in life. People may have both LATE and AD.

Part of the value of the ADRCs is that they 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 (genetics), 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,[1305] and these lifestyle factors are being actively and rigorously 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.

[1300] https://www.nia.nih.gov/health/what-lewy-body-dementia-causes-symptoms-and-treatments
[1301] https://www.nia.nih.gov/health/what-are-frontotemporal-disorders
[1302] https://www.nia.nih.gov/health/vascular-dementia
[1303] https://www.nia.nih.gov/health/what-is-dementia
[1304] https://www.nia.nih.gov/health/alzheimers-and-dementia/what-limbic-predominant-age-related-tdp-43-encephalopathy-late
[1305] https://www.nih.gov/news-events/news-releases/combination-healthy-lifestyle-traits-may-substantially-reduce-alzheimers

Burden of Illness

An estimated 6.7 million Americans, most of them age 65 or older, are living with AD, the most common form of dementia.[1306] Many others have an AD-related form of dementia. Experts agree that these numbers will increase significantly, potentially doubling by 2060, if no effective prevention or treatment methods emerge and current U.S. demographic trends continue. The greatest risk factor for AD 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 from around 63 million to about 82 million people in the next 25 years.[1307] 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 2025 (in 2025 dollars) for all individuals with AD/ADRD are estimated at $384 billion, not including the value of informal caregiving. Medicare and Medicaid are expected to cover $246 billion, or 64 percent, of the total health care and long-term care payments for people with AD/ADRD. Out-of-pocket spending is expected to be $97 billion, or 25 percent of total payments.[1308] Dementia-related costs are expected to rise dramatically in the coming decades as the baby boom generation continues aging.

Scope of NIH Activities: Research and Programmatic

Although research on AD has long been a cornerstone of NIA's research portfolio, NIH's efforts to better understand and treat AD/ADRD entered a new and significantly expanded phase in 2011 with the passage of the bipartisan *National Alzheimer's Project Act (NAPA)*.[1309] In October 2024, the *NAPA Reauthorization Act* was signed into law to continue coordination of federal planning, programs, and other efforts to address AD/ADRD through 2035. NAPA calls for a *National Plan to Address Alzheimer's Disease*, which was first developed in 2012 and has been subsequently updated each year.[1310] The Plan outlines objectives and sets milestones toward achieving six ambitious goals to both prevent future cases of AD/ADRD and to better meet the needs of the millions of American families currently facing these diseases. NIH progress toward achieving the research milestones that have been developed under the auspices of NAPA is tracked through periodic review of the research funded, results achieved, and new initiatives and programs. Progress is reported through the NIA's AD+ADRD Research Implementation Milestones Database.[1311]

Planning for AD research expenditures evolved with the *Consolidated and Further Continuing Appropriations Act, 2015* which mandated the NIH Professional Judgment Budget for Alzheimer's and

[1306] https://www.cdc.gov/alzheimers-dementia/about/index.html
[1307] 2023 National Population Projections Tables: Main Series. Table 2: Projected Population by Age Group and Sex. U.S. Census Bureau. Washington, DC. Revised July 2022. (https://www.census.gov/data/tables/2023/demo/popproj/2023-summary-tables.html)
[1308] https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf
[1309] http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf
[1310] https://aspe.hhs.gov/sites/default/files/documents/dc2ff0be0e08df15971fce57cb8e5c7a/napa-national-plan-2024-update.pdf
[1311] https://www.nia.nih.gov/research/milestones

Related Dementias (then presenting a budget for FY17). The Professional Judgment Budget is developed each year and presented without modification through the traditional federal budget process, providing 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 over the past decade informing the annual development of this budget include the following:

- AD Research Summits: 2015, 2018, 2021, and 2024
- AD/ADRD Summits: 2016, 2019, and 2022
- AD Care Services and Support Summits: 2017, 2020, and 2023
- Annual AD/ADRD Research Implementation Milestones

In addition, the ADRC network provides an infrastructure to facilitate activities across NIA signature programs, such as the Alzheimer's Disease Neuroimaging Initiative, Accelerating Medicines Partnership® Program for Alzheimer's Disease (AMP-AD), and the Alzheimer's Clinical Trials Consortium (ACTC).[1312,1313,1314] 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.

Resources shared from the ADRCs include data (through the NACC), biological samples (through the NCRAD), and brain MRI and PET scans (through Standardized Centralized Alzheimer's and Related Dementias Neuroimaging). They also facilitate targeted participant recruitment into clinical research studies, including clinical trials.

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 a broad range of populations with respect to ethnicity, race, and geography. 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 53,000 participants enrolled since 2005. In 2024, the Centers implemented a new form focused on AD/ADRD-disease modifying drugs as well as new concepts throughout the uniform dataset including subjective cognitive decline, mild behavioral impairment, and a verbal learning test to assess additional cognitive domains.

In 2013, NACC began accepting voluntary contributions of brain images from ADRCs. More than 11,000 images from more than 5,800 participants are now included in the database. These images are linked with

[1312] https://www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc
[1313] https://adni.loni.usc.edu/
[1314] https://adknowledgeportal.synapse.org/Explore/Programs/DetailsPage?Program=AMP-AD

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)[1315] when that data becomes available and when appropriate consent has been obtained. Further information is available on the NACC website.

In recent years the NACC database has undergone a transformation to modernize, upgrade, and update its database, which is one of the largest and most comprehensive databases of its type in the world. Multimodal data collected by the ADRCs are freely available through NACC 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

The NCRAD has substantially augmented its support for the research field by expanding the numbers and types of samples it collects and distributes. It also added a biomarker assay laboratory that centralizes and standardizes biomarker assays, as well as enabling cross-laboratory comparability studies. Hosted by Indiana University, NCRAD collects and shares blood, DNA, cell lines, and other biospecimens from more than 129,000 research participants at the ADRCs and in other NIA-funded studies.[1316] More than 420,000 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 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 Standardized Centralized Alzheimer's and Related Dementias Neuroimaging[1317] initiative with the goal of standardizing the acquisition, curation, and analysis of PET and MRI images acquired through the ADRCs. The images are processed for quality assurance and harmonization and further analyzed. 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/ADRD 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

[1315] https://www.adgenetics.org/
[1316] https://ncrad.iu.edu/
[1317] https://scan.naccdata.org/

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 NACC has data on more than 18,000 deceased participants whose brain tissue and associated data is available to researchers. More than 8,150 neuropathology exams were completed involving 58 percent of deceased participants. This valuable resource has contributed tremendously to research in AD/ADRD and to the many different causes of cognitive impairment.

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, Alzheimer's Clinical Trials Consortium, and Alzheimer's Disease Neuroimaging Initiative, as well as for clinical trials. Collaborations include ongoing interactions with organizations such as the Alzheimer's Association, the HHS Administration on Aging, and NIH's Alzheimer's Disease Education and Referral Center.

The Alzheimer's and Dementia Outreach, Recruitment, and Engagement Resources (ADORE) website,[1318] unveiled in 2019, continues to help advance research. It is a repository of materials submitted by ADRCs and other organizations to support recruitment and retention of participants for clinical trials and studies. The website 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,[1319] along with its companion Recruitment Planning Guide,[1320] which was released in October 2018.

NIH Funding for FY22, FY23, and FY24

NIH Funding of ADRCs for the reporting period was: $102.6 million in FY22, $103.7 million in FY23, and $114.7 million in FY24.

FY22, FY23, and FY24 Progress Report

Programmatic Activities and Outcomes

[1318] https://www.nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources
[1319] https://www.nia.nih.gov/research/recruitment-strategy
[1320] https://www.nia.nih.gov/sites/default/files/2019-05/ADEAR-recruitment-guide-508.pdf

Programmatic accomplishments for the ADRCs include the following examples:

- *Developmental Projects.* The ADRCs provide opportunities for investigators to start a research project each fiscal year. Over 230 developmental projects have been awarded by ADRCs between 2019 and 2024, most of which explore 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 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. 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 are one particular focus. Since 2018, more than 1,600 scholars and trainees ranging from high school students to junior faculty, have been provided with educational activities.

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. Topics range from the disease's biology to its impact on family and society and include 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:

- *Enhancing dementia research through collaboration, standardization, and sharing of resources.* A key component of the ADRCs is the ADRC Consortium for Clarity in AD/ADRD Research Through Imaging.[1321] This multisite imaging observational study occurs at the ADRC sites and was established to address important scientific gaps that the ADRCs could rapidly and uniquely fill by incorporating standardized PET and MRI protocols into each center's research visit schedule. The study seeks to leverage established national resources through close collaborations and will utilize the NACC's infrastructure to accelerate and track MRI and PET image submissions from the ADRCs and to make image analysis and summary results available to AD/ADRD researchers. The consortium of ADRCs have the unique expertise and capacity to conduct this study and work together to ensure its success and its impact on the field.
- *Potential role of peripheral immune response in AD.* Several peripheral immune-related genetic variants, including the cell membrane receptor TREM2 and its soluble form, sTREM2, are

[1321] Mormino EC, et al. Alzheimers Dement. 2025 Jan;21(1):e14383. Epub 2024 Nov 26. PMID: 39588767.

connected to AD. This is evidenced by sTREM2 being elevated in the cerebrospinal fluid in the early stages of AD and associated with slower cognitive decline in a disease stage-dependent manner. Scientist at the Cleveland Alzheimer's Disease Research Center examined how plasma sTREM2 and inflammatory activity are related across different stages of AD and found that the inflammation patterns change depending on the disease stage.[1322] The findings suggest that anti-inflammatory treatment use that targets the immune response in individuals with early-stage AD may be a feasible treatment approach to explore further.

- *Improvement in Cognitive Function After Kidney Transplantation.* Cognitive impairment among individuals with kidney disease can have negative personal and societal effects related to self-esteem, ability to work, quality of life, health care costs, and death. Further, there is a paucity of evidence-based research available on whether kidney transplantation improves cognitive function. Researchers at the University of Kansas Alzheimer's Disease Research Center examined the effect of kidney transplantation on different cognitive domains by assessing cognition before and at three- and 12-months post kidney transplantation.[1323] They found that episodic and verbal declarative memory became normal with kidney transplantation; and while semantic memory, verbal fluency, language, psychomotor speed, and visuospatial function showed improvement, it did not achieve normal levels. The findings suggest that cognitive impairment in kidney disease is partly reversible. Enhanced understanding of reversible versus irreversible cognitive impairment is important to the clinical care of patients before and after kidney transplantation.
- *Machine learning helps predict development of other chronic diseases in people with AD/ADRD.* Multiple chronic conditions are common among people with AD/ADRD, who often have two or more chronic conditions. There is a growing body of research on the patterns of multiple chronic conditions in AD/ADRD; however, few studies have examined the synergistic interactions of multiple chronic conditions with other factors in people with AD/ADRD. Mayo Clinic Alzheimer's Disease Research Center investigators used a machine learning prediction model and data from the National Alzheimer's Coordinating Center to examine patterns between multiple chronic conditions and AD/ADRD factors in 11,538 patients with 18 different multiple chronic conditions who visited the Center a combined 40,290 times.[1324] Results demonstrated that after some adjusting for individualized AD/ADRD factors, the machine learning models can predict which disease is developing in people with AD/ADRD based on their existing multiple chronic conditions patterns. Identifying and preventing specific multiple chronic conditions may be feasible with machine learning.
- *Impact of Hypertension with and without Diabetes on AD Risk.* Chronic diseases like hypertension and diabetes, which often co-occur, are leading risk factors for AD and are each associated with AD biomarkers. More research is needed to understand whether the risk of AD among individuals with hypertension differs with and without diabetes. Researchers assessed the risk of developing AD in cognitively normal individuals with hypertension who either had diabetes or did not have

[1322] Weber GE, et al. J Immunol. 2022 May 15;208(10):2283-2299. Epub 2022 May 6. PMID: 35523454.
[1323] Gupta A, et al. Am J Kidney Dis. 2024 Jul;84(1):28-37.e1.Epub 2024 Feb 28. PMID: 38423160.
[1324] Yew PY, et al. Alzheimers Dement. 2024 Jul;20(7):4818-4827. Epub 2024 Jun 11. PMID: 38859733.

diabetes.[1325] They found an increased risk of AD for both participants with hypertension who had diabetes and those with hypertension who did not have diabetes. However, post-mortem analysis of deceased participants found a neuropathological difference between the two groups. AD risk was higher among the participants with hypertension and diabetes who had AD neuropathology and cerebral amyloid angiopathy. Among the participants with hypertension who did have diabetes, AD risk was greater in participants with cerebrovascular neuropathology. These findings suggest different AD risk-reduction treatment will be necessary for patients with hypertension who have diabetes compared to those without diabetes.

- *Machine learning helps diagnose AD using clinical and MRI measurements.* Early diagnosis of AD is critical for early intervention and positive health outcomes. While machine learning models present some potential in making clinical diagnoses of AD in living persons, more work is needed to validate the use of these models to ensure accuracy by comparing their results against more accurate postmortem AD diagnoses. Researchers trained machine learning models to categorize the presence or absence of severe AD neuropathology from autopsies using MRI measurements from AD regions of interest, apolipoprotein E genotype, and demographic variables.[1326] The models achieved 84 percent accuracy in classifying severe AD neuropathology presence or absence and 70 percent accuracy in positively categorizing the presence of amyloid in living persons. The findings highlight the potential of machine learning models to use clinical and MRI information to classify the existence or non-existence of AD neuropathology in living persons.
- *Modeling amyloid accumulation to characterize AD progression.* AD is a neurodegenerative disorder that worsens over time. Understanding the long-term path of the disease, including the ability to predict the onset of clinical and cognitive symptoms, is important in developing effective treatments. Researchers developed and tested three methods to model the longitudinal course of amyloid accumulation, a known marker of AD, in three groups of participants using amyloid PET imaging.[1327] They found that the methods produced similar predictions and estimated ages of amyloid onset, and that the apolipoprotein E genotype (known to be associated with AD) and sex of the participant were both associated in different ways to the timing of amyloid onset and/or impairment onset. These findings provide insights into the feasibility of modelling longitudinal amyloid accumulation to characterize the course of AD at the individual level and will help to inform future research on factors that may impact the timing of clinical symptoms and the progression of AD.

Recommendations for Improving ADRCs Effectiveness, Efficiency, and Outcomes

Evaluation Plans

The National Advisory Council on Aging (NACA) evaluates and makes recommendations for the ADRC program every four years through its overall review of the Division of Neuroscience, with the next

[1325] Ruthirakuhan M, et al. Alzheimers Dement. 2024 Apr;20(4):2766-2778. Epub 2024 Feb 29. PMID: 38425134.
[1326] Zhuang X, et al. J Alzheimers Dis. 2024;100(3):843-862. PMID: 38943387.
[1327] Betthauser TJ, et al. Brain. 2022 Nov 21;145(11):4065-4079. Erratum in: Brain. 2023 Feb 13;146(2):e11. PMID: 35856240.

evaluation tentatively planned for 2027. In addition, 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.

Future Directions

NIH plans to have the ADRCs further develop research to enhance understanding of 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,[1328] a particular focus will be on the etiology, diagnosis, and treatment of mixed dementias. In addition, the ADRCs will search for new biomarkers – particularly blood biomarkers – 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 advance understanding of the risk factors that contribute to differences in health outcomes among populations, and how these differences are linked to disease process and high disease burden in different populations. Lastly, the ADRCs will evaluate the implementation of AD treatments across the Centers and study the impact FDA approved AD treatments have on the trajectory of the disease.

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
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

[1328] Boyle PA, et al. *Ann Neurol* 2017;83(1):74-83. PMID: 29244218.

Institution and Location	Year Established
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
Duke/University of North Carolina, Durham, NC	2021
University of Alabama, Birmingham, AL	2024
University of New Mexico, Albuquerque, NM	2024

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 older adults 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, around 63 million Americans are 65 years of age or older. Of these, about seven million are 85 and older, and more than 100,000 have reached 100 years of age. By 2050, the number of individuals aged 65 or older could reach 82 million. The number of the oldest of the old, people aged 85 or older, is expected to more than double to around 17 million by 2050.[1329] 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 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[1330] and other NIA-funded programs and centers (e.g., Resource Centers for Minority Aging Research,[1331] Centers on

[1329] 2023 National Population Projections Tables: Main Series. Table 2: Projected Population by Age Group and Sex. U.S. Census Bureau. Washington, DC. Revised July 2022. (https://www.census.gov/data/tables/2023/demo/popproj/2023-summary-tables.html)
[1330] https://www.rccn-aging.org/
[1331] http://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar

the Demography and Economics of Aging,[1332] Roybal Centers,[1333] Alzheimer's Disease Research Centers,[1334] and Nathan Shock Centers[1335]).

- 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 FY22, FY23, and FY24

NIH funding for the OAICs was $19.0 million in FY22, $19.6 million in FY23, and $19.5 million in FY24.

FY22, FY23, and FY24 Progress Report

Programmatic Activities and Outcomes

NIA supports 15 Older Americans Independent Centers that work together on multicenter research projects, shared core facilities, joint training programs, data harmonization initiatives, and collaborative grant applications. These efforts enhance resource sharing, standardize methodologies, and foster impactful, large-scale studies. Following are highlights of the research being done at these OAICs:

- 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. Researchers examine these issues from interdisciplinary perspectives across the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral and social sciences, and epidemiology.
- The Boston OAIC fosters collaborations among multidisciplinary teams of investigators from Harvard Medical School, Boston University, and Tufts University to foster function-promoting therapies, or pharmacologic, physical, nutritional, technological, and behavioral interventions that reduce the burden of disabling functional limitations in older adults.
- The University of Pittsburgh OAIC provides support and resources for investigators to identify interventions to optimize mobility and balance and prevent fall-related injuries in older adults. 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 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

[1332] http://www.nia.nih.gov/research/dbsr/centers-demography-and-economics-aging
[1333] http://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging
[1334] http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers
[1335] http://www.nia.nih.gov/research/dab/nathan-shock-centers-excellence

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 conditions. 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 function.
- 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.
- The University of Texas Health Science Center at San Antonio focuses on the translation of basic research findings into clinical interventions that will benefit older Americans. Current pilot projects include both preclinical and clinical studies.
- The Northwestern University OAIC seeks to improve primary care management for older, more medically complex adults with multiple chronic conditions. (According to the Centers for Disease Control and Prevention, around 79 percent of adults aged 65 and older have two or more chronic health conditions.[1336])

[1336] Watson KB, et al. Prev Chronic Dis. 2025 Apr 17;22:E15. PMID: 40245168 (https://www.cdc.gov/pcd/issues/2025/24_0539.htm)

- The University of Connecticut OAIC focuses on precision gerontology to enhance understanding of the growing heterogeneity of aging through targeted interventions, recognizing the wide variability among how individuals age.

Research Activities and Outcomes

- *Calorie Reduction May Help to Slow Aging in Healthy Adults.* Research to extend lifespan has examined dietary, genetic, physiological, and cellular strategies. NIA-funded researchers across multiple OAICs examined data from the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trial to determine the effect of calorie restriction on the aging process.[1337] CALERIE is a multicenter, randomized controlled trial conducted at three clinical centers. Over a two-year period, the CALERIE trial assessed calorie restriction in young and middle-aged adults who were healthy, lean, or slightly overweight, to identify any molecular changes related to aging. Trial participants reduced their calorie intake by a modest 12 percent. The calorie restriction group slowed their pace of aging by 2-3 percent based on the DunedinPACE measure, a DNA methylation-based "speedometer" which estimates the annual rate of biological aging. The researchers note that although the effect was small, the findings suggest that calorie restriction can have a positive long-term impact on the pace at which the body ages.
- *Improving Medication Management Among Older Adults with Cognitive Impairment.* Older adults with cognitive impairment who live alone often have trouble managing medications, placing them at increased risk for harmful medication effects. NIA OAIC-funded researchers used data from the National Health and Aging Trends Study and Medicare claims to assess the frequency and types of medications used by older adults with cognitive impairment.[1338] They focused on those medications that could either lead to adverse cognitive effects or be harmful if misused. The study found that participants who lived alone used an average of five medications, with 46 percent taking at least one high-risk medication. The results provide evidence that can inform the development of medication management interventions for older adults.
- *Personalized Risk-Reduction Strategies for Cognition and Dementia Among Older Adults.* Although some risk factors for ADRD such as physical inactivity, uncontrolled hypertension, and poor sleep are modifiable, more research is needed to identify strategies to reduce ADRD risks. Researchers at the University of California, San Francisco, OAIC, explored whether a personalized, multidomain risk reduction intervention could improve cognition and dementia risk among older adults.[1339] Investigators enrolled 172 participants in a randomized clinical trial who had a high risk of dementia based on a review of their electronic health record for diagnosis codes, blood pressure values, and lab results, as well as at least two other ADRD risk factors. The findings revealed that participants receiving the intervention had modest improvements in cognition, targeted risk factors for dementia, and quality of life, compared to the control group. Researchers also noted marked improvements in sleep, depressive symptoms, social satisfaction, and diabetes control in the intervention group. The study provides evidence that could be useful in shaping future interventions aimed at reducing modifiable risks that could lead to dementia in older adults.

[1337] Waziry R, et al. Nat Aging. 2023 Mar;3(3):248-257. Epub 2023 Feb 9. Erratum in: Nat Aging. 2023 Jun;3(6):753. PMID: 37118425.
[1338] Growdon ME, et al. J Am Geriatr Soc. 2024 Dec;72(12):3719-3729. Epub 2024 Jul 26. PMID: 39056523.
[1339] Yaffe K, et al. JAMA Intern Med. 2024 Jan 1;184(1):54-62. PMID: 38010725.

- *Lipid Deficiency as a Causal Factor for Bladder Disorder in Alzheimer's Disease.* AD progression may be associated with the loss of function in organs besides the brain and spinal cord, also known as peripheral organ dysregulation. There is a lack of understanding about the underlying causes of AD-associated peripheral organ dysregulation, such as the inability to control bladder activity. OAIC scientists at the University of Texas Health Science Center, in San Antonio, investigated changes in the lipidome (number and types of fat molecules) in the spinal cord of individuals with AD, using quantitative shotgun lipidomics, a tool to identify all the different types and numbers of lipids in biological samples.[1340] Researchers assessed spinal cord samples from deceased persons with and without AD and found that individuals with AD had noticeable reduction in myelin lipid, which is involved in nerve cell function, in the spinal cord, compared to individuals with no cognitive disorder. Further, there was a strong association between low sulfatide (one of the lipids that makes up myelin) levels and increased severity of AD. Researchers then made a mouse model unable to produce sulfatide and found the mice had significant spinal cord dysfunction and enlargement of the bladder. The study identified central nervous system sulfatide as a cause of lipid dysregulation, inflammatory response, and the development of bladder disorders associated with AD, and suggests that a treatment that aims to maintain sulfatide may prevent or treat peripheral disorders linked to AD.
- *Improving Sleep Quality May Improve Physical Performance in Older Adults After Hospitalization.* Inadequate sleep affects optimal functioning, both physical and mental. Sleep is especially critical to healing and recovery following a hospital stay, but few studies have investigated the impact of sleep quality on physical functioning after hospitalization in older adults. Researchers at the OAIC University of Texas Medical Branch conducted a study with older adult patients admitted for a cardiovascular, pulmonary, or metabolic condition and who had a short-term hospital stay.[1341] The goal was to investigate the association between sleep quality and functional recovery after hospitalization. Baseline data was collected before discharge with follow-up completed at four weeks after discharge. Results found that improvement in sleep quality was associated with improved physical functioning and independence after acute hospitalization. The findings suggest that older adults can regain physical functioning and independence following brief hospitalization with interventions that focus on sleep quality, fatigue, and daytime dysfunction.
- *Impairment in Sense of Smell a Biomarker of Frailty in Older Adults.* Sensory impairments, including olfactory (sense of smell) dysfunction, have been implicated as potential markers of frailty. Olfactory dysfunction has a high prevalence among older adults and is associated with dietary intake, quality of life, social interactions, mental health, and mortality. Despite being a common early sign of neurodegenerative disease and cognitive decline, the relationship between olfactory dysfunction and frailty is understudied. OAIC researchers at Johns Hopkins University investigated the association between sense of smell and frailty using data from the National Social Life, Health, and Aging Project and found that olfactory dysfunction is associated with frailty.[1342] This suggests that impairment in sense of smell is a potential biomarker and risk factor for frailty in older adults. The findings emphasize the importance of olfactory function in healthy aging and suggest that olfactory dysfunction might be integrated into frailty assessment tools.

[1340] He S, et al. Clin Transl Med. 2023 Jul;13(7):e1332. PMID: 37478300.
[1341] Arentson-Lantz EJ, et al. Front Sleep. 2022;1:1011930. Epub 2022 Oct 14. PMID: 37251511.
[1342] Nagururu NV, et al. J Gerontol A Biol Sci Med Sci. 2023 Jul 8;78(7):1276-1283. PMID: 36502375.

- *Better Health Prediction by Identifying Biological Age.* Biological age is a better indicator of a person's health than chronological age, but currently available molecular fingerprints to determine biological age are inadequate. OAIC Researchers at the University of Pittsburgh developed the Healthy Aging Metabolic (HAM) index to predict healthy aging by analyzing a combination of metabolites (small molecules in the body) and inflammatory markers from the blood of healthy older adults and younger adults with poor physical function.[1343] The researchers identified a panel of 25 metabolites that were most strongly correlated with healthy aging, such as those related to fatty acid metabolism (how the body uses fat molecule), the tricarboxylic acid cycle (molecular pathway that converts food into energy), and amino acids (molecules that make up proteins). These metabolites form the basis of the HAM index, which was also validated in an independent cohort of study participants. These findings suggest that a network of metabolic pathways and inflammatory markers can help predict biological age and better guide interventions for healthier aging.

Recommendations for Improving OAICs Effectiveness, Efficiency, and Outcomes

In 2023, the NACA reviewed the NIA Division of Geriatrics and Clinical Gerontology, where the OAICs are administratively housed, and made several recommendations,[1344] including the following:

- Enhance efforts to promote cross-disciplinary research between biological, clinical, social, economics, engineering, and behavioral sciences by including clearer guidelines and strategies.
- Continue to leverage partnerships by supporting interactions of the Claude D. Pepper Centers with other NIA-sponsored centers and Centers supported by other NIH Institutes and Centers.
- Conduct a strategic review of the program to identify ways to reduce regulatory and administrative burden on the centers, as well as provide additional funding to optimize center productivity, such as determining the most appropriate number of centers, funding level per center, and duration of awards.

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 better achieve its stated goals. NIA may also conduct its own independent evaluations of the OAIC program, as it did in 2023. The high-level findings of this evaluation showed that while the OAICs are meeting the program goals, there were a few areas of opportunity related to variability in data collection and collaboration. For example, the evaluation found that grantees who received pilot awards were applying for and receiving subsequent funding. By 2023, NIA had supported a total of 451 trainee research projects across all OAICs and an average of 32 trainee projects

[1343] Hamsanathan S, et al. Aging Cell. 2024 Apr;23(4):e14104. Epub 2024 Mar 7. PMID: 38454639.
[1344] https://www.nia.nih.gov/about/naca

per year. Lastly, the Coordinating Center was instrumental in facilitating collaborations across OAICs and outside networks with opportunities to continue strengthening and expanding collaborations.

Future Directions

NIH plans for the Claude D. Pepper OAICs to continue to develop and strengthen key areas of aging research to discover new and effective ways to promote independence in older age. NIH plans to continue offering competing OAICs the opportunity to propose the new optional Community Engagement Core to help promote recruitment and dissemination efforts and to better inform the design of OAIC-supported research studies.

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[1345]
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

Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

Establishment of the Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

The *Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act*, P.L. 107-84) included provisions for expanding and intensifying research on the muscular dystrophies and mandated that NIH establish Centers of Excellence for muscular dystrophy research. In the *Omnibus Appropriations for FY04* (P.L. 108-199), Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs), in honor of the former Minnesota senator who was a driving force behind the MD-CARE Act. The *Paul D. Wellstone Muscular Dystrophy*

[1345] A Center for the Study of Aging was started at Duke University in 1955; it was designated a Claude D. Pepper OAIC in 1992.

Community Assistance, Research, and Education Amendments of 2008 (P.L. 110-361) officially renamed the centers.

How the Wellstone MDCRCs Function Within the NIH Framework

Centers active in FY22 to FY24 are listed in Table 3. NIAMS, NICHD, and NINDS historically have funded up to six Wellstone MDCRCs. NHLBI has also co-sponsored competitions for Wellstone MDCRCs since 2007. NHLBI co-funds two centers and plans to support future MDCRC projects, contingent on the availability of funds and meritorious applications that align with NHLBI's mission.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles.[1346] Many dystrophies also affect other organ systems, such as the heart, brain, blood vessels, and gastrointestinal tract (stomach and intestines). Some forms occur in infancy or childhood, while others typically appear in middle age or later. The Wellstone MDCRCs address a variety of muscular dystrophies, including the following:

- *Duchenne and Becker muscular dystrophies (DMD and BMD).* 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 with DMD typically produce little or no functional dystrophin, which muscle cells need to function properly. DMD usually becomes evident when a child begins walking. Boys with DMD typically require a wheelchair by ages 10 to 12. Life expectancy in this group is now in the 30s or beyond, with the disease ultimately leading to life-threatening cardiac or respiratory complications. BMD, a less severe disease, occurs when the body produces low levels of dystrophin or forms of dystrophin that do not have full function.
- *Myotonic dystrophies.* Myotonic dystrophy types 1 and 2 are commonly adult muscular dystrophies, although forms of these diseases can affect newborns and other children. They are marked by myotonia (an inability to relax muscles after they contract) and muscle wasting and weakness. Myotonic dystrophy's severity and symptoms vary. They can affect skeletal muscles and other body systems, including the heart, endocrine organs (organs that release hormones into the bloodstream), eyes, brain, and gastrointestinal tract.
- *Facioscapulohumeral muscular dystrophy (FSHD).* FSHD initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral). Symptoms usually develop in the teenage years. Some affected individuals become severely disabled. Wasting of muscles of the trunk can lead to life-threatening breathing complications.
- *Congenital muscular dystrophies (CMDs).* The CMDs are a group of muscular dystrophies with different genetic causes that are either present at birth or become evident before age two. Several forms are caused by defects in the interactions of muscle cells with the surrounding extracellular matrix. The CMDs often affect the brain and other organs.

[1346] https://www.ninds.nih.gov/health-information/disorders/muscular-dystrophy

- *Limb-girdle muscular dystrophies (LGMDs).* All LGMDs show a similar distribution of muscle weakness, affecting both upper arms and thighs. Scientists have identified many forms of LGMDs caused by mutations in many different genes; some affect children, and others affect adults. A genetic diagnosis is confirmed in only about half of people with LGMD, suggesting that other genes associated with this condition have not yet been identified.

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. For example, in 2023 the FDA approved the steroid vamorolone as a better-tolerated alternative to corticosteroids for treating DMD, particularly for long-term use; in addition to approving a gene therapy for young boys who have a confirmed mutation in the DMD gene. The gene therapy was expanded to include older individuals in 2024, along with the approval of givinostat, which inhibits fibrosis and fat accumulation in muscle, reduces inflammation, and promotes muscle regeneration in people with DMD. 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 7,000 males aged 5-24 has DMD or BMD (males are more likely to be affected than females). Myotonic dystrophy affects approximately 1 in 10,000 people and affects men and women equally. FSHD affects approximately 1 in 25,000 people and affects men and women equally. Determining the prevalence of LGMDs is difficult because their features vary and overlap with those of other muscle disorders. They are estimated to affect 1 in 50,000 individuals, and males and females are also affected equally.[1347]

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs promote communication and collaboration, develop and share research resources, and help train new muscular dystrophy researchers. Each center can conduct a mixture of basic research to understand the diseases, translational research to turn basic research findings into interventions, and clinical studies to determine how the diseases affect people and to test interventions. The overall focus of the Wellstone MDCRCs is to integrate activities to develop therapies and other strategies to reduce the impact of disease on people living with muscular dystrophies and their families.

Collectively, the Wellstone MDCRCs conduct research on various forms of muscular dystrophy, including some not listed above. Examples of research topics addressed by the Wellstone MDCRCs in FY22, FY23, and FY24 follow:

[1347] https://www.cdc.gov/muscular-dystrophy/types/index.html

- At the University of Rochester MDCRC, 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 was funded through August 2024, at which point it successfully competed for funding in collaboration with the University of Florida. The University of Florida/University of Rochester MDCRC is funded through July 2028.
- Research at the University of Iowa MDCRC focuses on understanding the causes of and developing treatments for a group of dystrophies called dystroglycanopathies, which are associated with defects in muscle proteins known as dystroglycans. These diseases include some LGMDs, CMDs, and Miyoshi myopathy. The center is funded through June 2025.
- Projects at a separate University of Florida MDCRC, which also include investigators from the University of California, Los Angles and Northwestern University, focus on the roles of inflammation, fibrosis, and fat infiltration in muscular dystrophy and on identifying strategies to counter these processes. The center is funded through July 2025.
- The Wellstone MDCRC at the University of Massachusetts continues to partner with investigators at Children's Hospital in Boston, the Kennedy Krieger Institute, and Children's Institute at Nationwide Children's Hospital on studies of molecular, genetic, and epigenetic pathologies of FSHD, with the goal of developing potential therapies that can be tested clinically. Funding for this center ended in 2024.
- The center funded through the University of Washington and Fred Hutchinson Cancer Research Center 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 2028.
- Investigators at the University of Texas Southwestern Medical Center (UT Southwestern) are exploring whether a technique that combines the CRISPR/Cas9 system of genomic editing with the ability to generate induced pluripotent stem cells could be used to treat DMD, including DMD-associated cardiomyopathy. This center is funded through August 2025.
- Research at Nationwide Children's Hospital Research Institute, the newest Wellstone MDCRC, focuses on the development of patient-derived reagents for the testing of new therapies intended to create the next generation of treatments beyond microdystrophin gene therapy (using a shortened, yet functional, version of the full-length dystrophin protein, which is too big for current gene therapy techniques). This center is funded through July 2028.

Each Wellstone MDCRC has core facilities that provide unique resources or services for the muscular dystrophy research community. Cores include repositories of research data and biologic samples from people 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 FY22, FY23, and FY24

NIH funding for the Wellstone MDCRC program was $9.1 million in FY22, $6.2 million in FY23, and $9.3 million in FY24.

FY22, FY23, and FY24 Progress Report

Programmatic Activities and Outcomes

Two Wellstone MDCRCs successfully competed for support in FY24: the University of Washington and Fred Hutchinson Cancer Research Center, along with a new center at Nationwide Children's Hospital Research Institute in Columbus, Ohio.

The Wellstone MDCRC program has provided opportunities for public–private partnerships in muscular dystrophy. Productive collaborations between the centers and patient advocacy groups continue to promote participation of affected individuals and a patient voice in the conduct of research. For example, the Iowa MDCRC hosts an annual conference of people living with dystroglycanopathies and their families, during which researchers provide updates on scientific advances and affected individuals provide data and biospecimens. Another example is the UT Southwestern MDCRC, which established the company Exonics Therapeutics to develop CRISPR-based gene editing therapeutics for DMD. The company was acquired by Vertex Pharmaceuticals to continue to advance this treatment strategy.

The Wellstone MDCRC 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. Data and Resource Sharing Plans are in place to report, request, and deliver core resources in a timely fashion. Examples of shared core facilities include the following:

- The University of Rochester's National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy contains information about more than 2,600 affected people, and provides researchers with cell and tissue samples and clinical information about the donors of these samples. Between 2018 and 2023, the registry facilitated 19 clinical studies which supplied data for educational or research purposes to 7 groups or studies.
- The University of Iowa Wellstone MDCRC oversees a Muscle Tissue/Cell Culture/Diagnostics Core that serves as a national tissue and cell culture resource for research, as well as a laboratory for patient diagnostic and post-intervention biopsy evaluation for clinical trials. A repository contains muscle biopsies from more than 9,000 affected individuals with various neuromuscular disorders. It also contains fibroblast cell cultures established from more than 450 people—predominantly those living with dystroglycanopathies—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. Especially relevant to Duchenne and LGMD, the facility has supported more than 80 different investigators from academia and industry and has received letters of support from 13 groups who stated the substantial value of the core.
- The University of Massachusetts Wellstone MDCRC supported a repository of tissues collected from patients with FSHD and unaffected relatives, which enabled studies of biomarkers and candidate drugs. It provided characterized FSHD cells and control muscle cells to laboratories studying FSHD or other muscular dystrophies. The center also provided animal models of FSHD to

the research community as part of its core facilities. As stated above, funding for this center ended in 2024.

- The University of Washington Wellstone MDCRC provides viral and plasmid vectors (for gene therapy), cell lines, and antibodies for studies involving the development and testing of potential therapies in small and large animal models. The facility has supplied 80 groups with virus (for gene therapy) and preparations to study various types of muscular dystrophy. Services offered include consulting, reagents, and training related to vector production.
- The UT Southwestern Wellstone MDCRC provides a comprehensive electronic database that scientists can use to optimize their gene editing experiments to make more precise and efficient DNA modifications to repair DNA sequences in cells from patients with muscular dystrophy. For example, scientists have functionally restored dystrophin protein levels in patients cells, and these unique cell lines are a valuable molecular biology resource available to physicians and scientists.
- The Cell Line and Tissue Bank Shared Resource Core at the Nationwide Children's Hospital MDCRC provides patient-derived cell lines to researchers, catalyzing the development of new therapies for a wide variety of disease-causing mutations.

Research Activities and Outcomes

The Wellstone MDCRCs conduct high-quality translational and clinical studies to advance understanding of and therapy development for a variety of muscular dystrophies. Several active clinical trials in the muscular dystrophies were made possible by Wellstone MDCRC findings. Discoveries by investigators affiliated with the Wellstone MDCRC programs also form a basis of new conceptual models, with potential impacts on therapy development for the dystrophies, other neuromuscular diseases, and additional conditions. Examples of accomplishments in FY22, FY23, and FY24 are provided below:

- Researchers at the University of Rochester MDCRC performed a prospective, longitudinal study of 113 adults with myotonic dystrophy type 1 (DM1) using computer-assisted evaluation of cognitive function along with measures of muscle function and patient-reported outcomes.[1348] The study demonstrated that people who have DM1 can have difficulties with their working memory, demonstrating the need for treatments that address cognitive and other CNS symptoms, as well as muscle function. This study demonstrates the feasibility of using computer-assisted measures of cognitive function in multisite studies of DM1.
- The University of Iowa MDCRC, in partnership with the FSHD Society, undertook a study in response to concerns from people living with FSHD about symptoms affecting swallowing, bowel, and urinary function.[1349] When comparing data collected from individuals with FSHD and people without FSHD who lived with them, the investigators found thatpeople with FSHD are more likely to experience symptoms related to swallowing, bowel, and urinary function. Furthermore, these symptoms negatively affected the quality of life of 34 percent of respondents. While the study did not provide data on the pathophysiologic causes of these symptoms, it documents the experience of people living with FSHD and could justify future mechanistic studies that could eventually lead

[1348] Deutsch GK, et al. *Muscle Nerve* 2022 May;65(5):560-567. PMID: 35179228.
[1349] Cole MR, et al. *Muscle Nerve* 2024 Mar;69(3):325-333. PMID: 38158588.

to therapies. This study highlights the direct impact that affected individuals have on the research questions that are being asked. It also demonstrates the important role those individuals play in research by providing their data to answer these important questions.

- Investigators at the University of Florida Wellstone MDCRC have advanced understanding about the pathology and role of abdominal muscles when exhaling and its relationship to cough and airway clearance capacity in people living with DMD.[1350] Forty study participants with DMD aged 6-18 years underwent longitudinal Magnetic Resonance Imaging of the abdomen to determine fat fraction in expiratory muscles. Fat fraction data, along with other factors, were used to estimate levels of muscle degeneration as evidenced by percentage of muscle being replaced by fat over a course of 36 months. Maximal inhaling and exhaling pressures and peak cough flow were also collected. These data improve understanding of the early phase of respiratory compromise in DMD, which typically presents as airway clearance dysfunction prior to the onset of hypoventilation, and links expiratory muscle fatty infiltration to pulmonary function measures.
- Researchers at the University of Massachusetts Wellstone MDCRC used an advanced, long-range sequencing technology to study in greater detail the region of the genome known to be involved in FSHD, including its length, genetic variations, and methylation patterns.[1351] Traditionally, genetic analysis of this DNA region, called D4Z4, had been difficult due to its large size and highly repetitive nature. This study demonstrates the potential of the new long-range sequencing technology as a tool to overcome those difficulties and aid in the clinical diagnosis of FSHD and the development of novel gene-based therapies.
- Wellstone MDCRC investigators at the University of Washington and the Fred Hutchinson Cancer Research Center developed an MRI approach that shows promise for use in clinical trials of patients with FSHD.[1352] Researchers conducted MRI scans and muscle biopsies of the tibialis anterior muscles (found in the lower leg near the shin) in patients with FSHD and found a strong association between the MRI findings and the expression of genes associated with FSHD. These findings provide a strong basis for including MRI and molecular biomarkers in clinical trial design.
- Investigators at the UT Southwestern Wellstone MDCRC identified multiple transcription factors—proteins that control gene expression—that are critical for stage-specific muscle fiber development. They also mapped cell signaling pathways that are affected in neuromuscular disease.[1353] These findings provide a transcriptional atlas of muscle development and reveal genetic links between muscle fiber formation, maturation, and contraction. The findings could inform future therapeutics and research targets for neuromuscular diseases.

Recommendations for Improving Wellstone MDCRCs Effectiveness, Efficiency, and Outcomes

Evaluation Plans

[1350] Barnard AM, et al. *Chest.* 2022 Mar;161(3):753-763. PMID: 34536384.
[1351] Butterfield RJ, et al. Genome Res. 2023 Sep;33(9):1439-1454. PMID: 37798116.
[1352] Wong CJ, et al. *Hum Mol Genet.* 2024 Apr 8;33(8):698-708. PMID: 38268317.
[1353] Dos Santos M, et al. *Nat Commun.* 2023 Jul 19;14(1):4333. PMID: 37468485.

NIH released an evaluation report in January 2019.[1354] Although NIH had refined the Wellstone MDCRC program since the program's inception in FY03, 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 FY22[1355,1356] and subsequent Notice of Funding Opportunities (NOFOs) and were reflected in the Notice of Awards, explicitly stating information that must be included in annual progress reports. For example, the NOFOs prominently emphasized biomarker development, validation of clinical outcome assessment measures, and natural history studies. The most significant changes to the NOFOs in response to the working group's evaluation centered on the training cores, especially interdisciplinary training and training for students and fellows at other Wellstone Centers and non-Wellstone institutions. Worth highlighting is the annual myology course (study of the muscular system), organized by the Nationwide Children's MDCRC, which is open to Wellstone Center and non-Wellstone clinical and lab-based trainees. This is the only workshop of its kind in the U.S., featuring a mix of basic and clinical science lectures followed by specific training in either clinical treatment protocols or basic science laboratory techniques. This course is now supported through the Wellstone Centers. The renewal process of the Muscular Dystrophy Coordinating Committee's new Action Plan in FY25 is underway and will likely prompt NIH staff to reflect on ways the Wellstone MDCRC program can be adjusted for future NOFOs to better address emerging needs and opportunities.

Future Directions

NIH is committed to supporting up to six outstanding Wellstone MDCRCs. Based on its funding commitment to the existing centers, NIH announced an open competition to fund up to three centers (for a total of up to six active centers) in FY25,[1357] based on the availability of funds and a sufficient number of highly meritorious applications. Strategic planning efforts by the Muscular Dystrophy Coordinating Committee have highlighted priorities for muscular dystrophy research, including understanding the mechanistic basis of patient population variation improving animal, cell, and tissue models. Those priorities will become areas of emphasis for future Wellstone Center NOFOs. The Wellstone MDCRCs will continue to disseminate NIH programmatic interests and funding opportunities throughout their network.

Table 3. Active Senator Paul D. Wellstone MDCRCs, FY22, FY23, and FY24

Institution and Location	Years Funded
University of Florida/Rochester, Gainesville, FL	2003–present
University of Iowa, Iowa City, IA	2005–present
University of Florida/ University of California, Los Angles /Northwestern, Gainesville, FL	2005–present
University of Massachusetts, Worcester, and Children's Hospital, Boston, MA	2013–2024

[1354] https://www.ninds.nih.gov/sites/default/files/documents/WellstoneCenterEvalRptExecSumm-508.pdf
[1355] https://grants.nih.gov/grants/guide/rfa-files/RFA-AR-23-001.html
[1356] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-23-032.html
[1357] https://grants.nih.gov/grants/guide/rfa-files/RFA-AR-25-002.html

Institution and Location	Years Funded
University of Washington and the Fred Hutchinson Cancer Research Center, Seattle, WA	2003–2009 2014–present
University of Texas Southwestern Medical Center, Dallas, TX	2015–present
Nationwide Children's Hospital Research Institute, Columbus, OH	2010–2017 2024–present

National Institute on Minority Health and Health Disparities Centers of Excellence

Establishment of NIMHD Centers of Excellence Program

The NIMHD Centers of Excellence (COE) program, established by the *Minority Health and Health Disparities Research and Education Act of 2000* (Public Law 106-525),[1358] has played a vital role in supporting the NIH and NIMHD mission. Tackling the complex drivers of health disparities requires a well-trained scientific workforce and a cross-disciplinary research framework that cuts across scientific and organizational silos to integrate multiple disciplines in biology, behavioral and social sciences, epidemiology, data science, public health, health services, economics, and clinical science. It also requires strong collaborations between researchers, community organizations, health service providers, public health agencies, policymakers, and other partners to ensure that relevant, contextually appropriate research is conducted; and more importantly, that findings can be translated into sustainable community and health system-level changes.

How the NIMHD COEs Function within the NIH Framework

NIMHD established the NIMHD COEs to create a comprehensive platform within academic institutions that would address health disparities in priority diseases and conditions by conducting research, training a talented and dedicated scientific workforce, and engaging the community.

NIMHD previously used the *U54 Specialized Center Cooperative Agreement* funding mechanism to address this need.[1359] This type of funding encourages close collaboration between NIH and researchers, with NIH staff being actively involved in guiding independent research projects. As described in greater detail below, the NIMHD COE program in FY24 shifted its focus to mentored research projects. With this increased focus on research education and training, NIMHD switched to using the *P50 Specialized Centers* funding mechanism which gives universities and research institutions more flexibility and independence in managing their projects.[1360]

NIMHD funded 15 COEs (Table 4) between FY22 and FY24. Several institutions continued their Centers of Excellence programs, including Arizona State University, Duke University, Johns Hopkins University, New

[1358] https://www.govinfo.gov/app/details/PLAW-106publ525
[1359] https://grants.nih.gov/funding/activity-codes/U54
[1360] https://grants.nih.gov/funding/activity-codes/p50

York University School of Medicine, University of Arkansas, University of Alabama at Birmingham, University of Illinois at Chicago, University of Miami Coral Gables, University of New Mexico, and the University of North Texas. New centers launched at Georgetown University, Icahn School of Medicine at Mount Sinai, State University of New York at Buffalo, University of Kentucky, and the University of Texas at El Paso.

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 reducing health disparities and improving health for all.

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 field of health disparities science provides a platform for research to advance and generate knowledge that can improve health and reduce the burden of diseases and conditions across populations. A health disparity is a largely preventable health difference that adversely affects populations who experience greater challenges to optimal health. Health disparities may be observed in the risks, prevalence, or burden for specific behaviors, as well as the incidence, prevalence, and mortality from conditions, diseases, and/or disorders. Health disparities also can be observed in health care access, quality, and utilization, and within the delivery of clinical care.

Health disparities can be identified based on significantly greater or disproportionate burden that is preventable on one or more of the following measures:

- Incidence and/or prevalence, including earlier onset of disease or higher prevalence of pre-clinical disease/biomarkers.
- Premature or excessive mortality from specific conditions.
- Population health or burden of disease metrics, such as life expectancy, disability adjusted life years, or health-related quality of life.
- Condition-specific symptoms on validated self-reported measures that reflect daily functioning in physical, cognitive, or socio-emotional domains.
- Prevalence of short-term and/or long-term preventable complications.
- Prevalence of modifiable risks, health risk behaviors, and adverse clinical outcomes.
- Inadequate, untimely or differential access, utilization, or availability of high-quality health care services.

Addressing health disparities in a meaningful way requires a comprehensive view of how health is maintained, improved, or worsened via modifiable influences. These factors include but are not limited to barriers to high-quality health care, adverse environmental and societal exposures (e.g., physical, chemical, and/or community-related elements), individual biological factors and reactions (e.g., age, inherited conditions, stress hormones, metabolic perturbations), gene expression (e.g., epigenetics) and lifestyle and behavioral factors (e.g., tobacco use, substance use, physical activity, food consumption, decision making).

Scope of NIH Activities: Research and Programmatic

Historically, NIMHD COEs were a comprehensive research platform in academic institutions that addressed health conditions and diseases that disproportionally affected populations that experience disparities through independent research projects, education, training, and community engagement. To reinforce alignment with statutory requirements, the NIMHD COE program in FY24 shifted its focus to mentored research projects in biomedical, behavioral, and clinical research for early-stage investigators, as well as other research education and training activities. The cardinal components of the COEs are:

- The *Administrative Core* provides overall scientific leadership and strategic direction for the Center of Excellence. It provides administrative oversight evaluation to ensure that research training and education activities are implemented per the proposed timelines, it monitors progress on pilot research projects, and it ensures that Center-supported activities are carried out in compliance with applicable federal regulations and policies.
- The *Investigator Development Core* offers career enhancement activities for investigators at all faculty levels of the institutions. These include seminars, workshops, and/or other activities that promote the development of scientific expertise. The *Investigator Development Core* also supports a Pilot Project Program that provides opportunities for postdoctoral fellows, junior faculty, and other early-stage investigators to further develop research training skills and expertise in health disparities research, with the goal of establishing their own independent research program.
- The *Community Engagement and Dissemination Core* facilitates collaborative and sustainable relationships with community organizations and other partners. The intent is the dissemination of findings from the pilot research projects and technical advice on how to translate research findings into sustainable changes at the local level that improve the health of population.

NIH Funding for FY22, FY23, and FY24

NIMHD funding for the COEs was $9.7 million in FY22 and $4.2 million in FY24, for a total of $13.9 million. No funds were awarded in FY23. Most funds ($9.7 million in FY22) were awarded through the U54 funding mechanism, while the P50 funding mechanism accounted for $4.2 million (in FY24).

FY22, FY23, and FY24 Progress Report

Programmatic Activities and Outcomes

Fifteen NIMHD COEs were active in FY22, FY23, and FY24 (Table 4).

Research Accomplishments

Research outputs from the NIMHD-funded COEs from FY22, FY23, and FY24, including several highlighted below, provide scientific evidence and progress on a range of critical health topics.

- *Implementation of a Telehealth Intervention for Rural Patients with Type 2 Diabetes*.[1361] Rural populations with type 2 diabetes face challenges in managing their condition due to limited access to specialized care. Researchers tested a telehealth intervention, Advanced Comprehensive

[1361] Kobe EA, et al. J Gen Intern Med. 2022 Sep;37(12):3080-3088. Epub 2022 Jan 3. PMID: 34981358.

Diabetes Care, which combined remote monitoring, patient self-management support, and specialist-guided medication management. Over six months, patients showed significant improvements in blood sugar control, which lasted for up to 18 months. This study demonstrated that comprehensive telehealth programs like Advanced Comprehensive Diabetes Care can effectively improve long-term blood sugar control in rural patients with hard-to-manage diabetes, offering a viable solution to overcome barriers to care in these communities.

- *Fostering a Healthy Food Environment May Reduce Cancer Disparities*.[1362] Dietary behaviors and excess body weight contribute to approximately 18 percent of cancer cases, disproportionately affecting communities with limited access to healthy foods. These populations often face higher rates of cancers linked to diet and obesity, such as colorectal, liver, and pancreatic cancer. Enhancing access to nutritious foods through targeted interventions could significantly reduce cancer disparities.
- *Using SI and Gene Expression Data Helps Identify Infants at Risk for Lung Disease*.[1363] Bronchopulmonary dysplasia (BPD) is a common lung disease affecting premature infants, leading to long-term respiratory issues. Early identification of infants at risk for BPD is crucial for timely interventions. Researchers developed a blood test using five specific genes to predict which premature infants would develop BPD. Analysis of blood samples from 97 very low birth weight infants using machine learning identified these genes with high accuracy. This advancement filled a critical need for early identification, which can improve long-term respiratory outcomes in premature infants.
- *The Role of Childhood Asthma in Obesity Development.*[1364] Childhood asthma may increase the risk of obesity, a critical public health concern. Researchers analyzed multiple cohorts of U.S. children and found that children with asthma had a 23 percent higher risk of becoming obese compared to peers without asthma. Notably, asthma medications reduced this risk, indicating effective asthma management could also prevent obesity. This study highlighted the importance of integrated healthcare strategies addressing both asthma and obesity prevention in children.
- *Maternal Mitochondrial Function May Contribute to High Blood Pressure During Pregnancy.*[1365] Hypertensive (high blood pressure) disorders like gestational hypertension and preeclampsia significantly affect maternal and infant health. Researchers examined how changes in mitochondrial genes—genes important for energy production—in mothers and infants might contribute to these conditions by analyzing maternal blood and placental samples. Results showed that altered mitochondrial gene activity in mothers was linked to inflammation, cell death, and issues with placental development. In infants, these changes correlated with increased cellular signaling. Understanding mitochondrial involvement can help develop targeted treatments, improving pregnancy outcomes.

[1362] Wolf PG, et al. Transl Behav Med. 2021 Dec 14;11(12):2123-2126. PMID: 34223908.
[1363] Moreira A, et al. Am J Physiol Lung Cell Mol Physiol. 2023 Jan 1;324(1):L76-L87. Epub 2022 Dec 6. PMID: 36472344.
[1364] Stratakis N, et al. Epidemiology. 2022 Jan 1;33(1):131-140. PMID: 34561347.
[1365] Ricci CA, et al. Physiol Genomics. 2023 Jul 1;55(7):275-285. Epub 2023 May 15. PMID: 37184228.

- *Mental Health Conditions Increase Risk of Severe Maternal Morbidity*.[1366] Perinatal (the weeks before and after giving birth) mental health disorders significantly contribute to severe maternal morbidity and increased healthcare costs. A study analyzing hospital data found that individuals with perinatal mental health conditions experienced 50 percent higher risks of severe maternal morbidity and increased hospitalization costs, totaling approximately $102 million annually in the U.S. Notably, those diagnosed with trauma- or stress-related mental health disorders experienced even higher hospitalization costs—$825 more per delivery—and 87 percent higher rates of severe maternal morbidity compared to individuals without these diagnoses. These findings highlighted the substantial economic and health burdens associated with perinatal mental health conditions, emphasizing the need for targeted interventions and resources to support affected individuals.

Recommendations for Improving NIMHD COEs Effectiveness, Efficiency, and Outcomes

Since the inception of the program in 2002, NIMHD COEs have advanced efforts to reduce health disparities. However, opportunities remain for further enhancing study designs, methodologies, and translation of research findings into practical interventions that improve the quality of life for all populations.

Recognizing that addressing health disparities requires collective action, NIMHD encourages COEs to strengthen existing and foster new strategic partnerships with other NIH-funded research centers and programs, federal agencies, academic institutions, healthcare organizations, community-based groups, and other entities.

Evaluation Plans

NIMHD program staff evaluate each COE's annual progress by examining their accomplishments related to the proposed Center goals, including 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 publications such as books and book chapters, sponsored conferences, research presentations, research training and professional development opportunities for emerging scientists, and community engagement activities—such as health fairs and forums, sharing health promotion materials, and community participation in research and clinical trials.

Future Directions

The NIMHD COE program will continue to pursue research efforts to improve societal health and understand, reduce, and eliminate health disparities, with an emphasis on sustaining current and establishing new partnerships. Through these partnerships, COEs will continue to generate valuable biomedical and behavioral insights to bridge knowledge gaps on a broad spectrum of diseases and conditions. Additionally, COEs will align with current research priorities, emphasizing the application of research findings into clinical practice.

[1366] Brown CC, et al. Health Aff (Millwood). 2021 Oct;40(10):1575-1584. PMID: 34606352.

The success of these and future efforts by the NIMHD COEs will rely on developing enhanced methodological tools, measures, validated instruments, and novel research designs to better understand the connections between biological, behavioral, and social factors in health disparities. Equally important is the development and implementation of evidence-based interventions to improve health outcomes. Strong collaboration with important partners, including community organizations, local government, and health care systems, will be essential to ensuring that research findings translate into meaningful clinical and community impact.

Table 4. NIMHD Centers of Excellence Active in FY22, FY23, and FY24

Institution	Title/ Center's Name	Activity Code	Project Number
Arizona State University Tempe Campus	The Southwest Interdisciplinary Research Center	U54	MD002316
Duke University	Duke Center for Research to Advance Healthcare Equity	U54	MD012530
Georgetown University	Development of Investigators Supporting Community Outreach and Value of Engagement in health disparities Research	P50	MD019487
Icahn School of Medicine at Mount Sinai	The Institute for Health Equity Research Catalyst Center	P50	MD019475
Johns Hopkins University	Johns Hopkins Center for Health Disparities Solutions	U54	MD000214
New York University School of Medicine	New York University Center for the Study of Asian American Health	U54	MD000538
State University of New York at Buffalo	Igniting Hope in Buffalo New York Communities: Training the Next Generation of Health Equity Researchers	P50	MD019473
University of Alabama at Birmingham	Obesity Health Disparities Research Center	U54	MD000502
University of Arkansas for Medical Sciences	Arkansas Center for Health Disparities	U54	MD002329
University of Illinois at Chicago	Center for Health Equity Research	U54	MD012523
University of Kentucky	Achieving Success in Community-Engaged research to eliminate Disparities	P50	MD019476
University of Miami Coral Gables	Center for Latino Health Research Opportunities	P50; U54	MD002266; MD019468
University of New Mexico Health Sciences Center	Transdisciplinary Research, Equity & Engagement Center	U54	MD004811
University of North Texas Health Science Center	Texas Center for Minority Health, Education, Research and Outreach	U54	MD006882
University of Texas El Paso	UTEP Center for Investigator Training and Community Engagement in Transdisciplinary Minority Health Disparities Research	P50	MD019494

Rare Diseases Clinical Research Network

Establishment of the Rare Diseases Clinical Research Network

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 withing NCATS) at NIH to enter into cooperative agreements with or make grants for regional centers of excellence on rare diseases. These Centers of Excellence were initiated in 2003 with the establishment of the Rare Diseases Clinical Research Network (RDCRN) and have been continually funded since that time.

The RDCRN's mission is to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment, and data sharing. Through the RDCRN consortia, physician scientists and their multidisciplinary teams work together with patient advocacy groups to study nearly 200 rare diseases at sites across the nation.

How RDCRN Functions within the NIH Framework

The RDCRN is a collaborative effort across ten NIH Institutes, Centers, and OD Offices (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 programmatic involvement by representatives from the participating NIH ICOs that provide funding to the network.[1367]

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 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.

[1367] https://ncats.nih.gov/research/research-activities/rdcrn

As of the end of 2024, the RDCRN has supported 31 consortia, with 19 of them currently active (see Table 5b). Between 2019 and 2024 the RDCRN has:

- Studied more than 200 diseases
- Conducted 80 clinical studies and 13 clinical trials
- Published 1,101 scientific publications
- Been cited in 16,958 academic publications and 80 policy documents

Through a competitive, meritorious peer review process, the RDCRN awards grants every five years. In 2024, the Network is in its fourth award cycle (RDCRN.4) since inception. The competition for the fifth cycle (RDCRN.5) was delayed by one year to allow RDCRN.4 investigators to complete clinical research that was interrupted by the pandemic. RDCRN.5 grants are scheduled to be awarded in FY25. To learn more about the RDCRN consortia and the DMCC, visit the RDCRN website.[1368]

Description of Disease or Condition

The *Rare Diseases Act of 2002* defines a rare disease as a condition affecting fewer than 200,000 individuals in the U.S. Collectively, over 10,000 diseases or conditions fall into this category. 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 affects a specific location in the body and is not simply a result of physical injury
- Conditions: a particular state of being that limits/restricts something else

Burden of Illness

While each individual disease or condition is rare; cumulatively, rare diseases are not rare, as approximately 30 million people in the U.S. have a rare disease.[1369] Most of these disorders are serious or life-threatening chronic conditions and lead to significant morbidity and mortality. Additionally, approximately 70 percent of rare diseases occur in childhood. Of those children, 30 percent die before the age of 5 years, making rare diseases a significant public health concern.

Rare diseases also represent a disproportionate share of health care spending. Total national spending on medical costs for rare disease patients is estimated at $400 billion per year,[1370] with a total economic burden of nearly $1 trillion.[1371]

The burden of illness for individual 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

[1368] https://rdcrn.org/
[1369] https://rarediseases.info.nih.gov/
[1370] https://www.healthaffairs.org/content/forefront/economic-burden-rare-diseases-quantifying-sizeable-collective-burden-and-offering
[1371] https://everylifefoundation.org/burden-landing/

data. Beyond the individual burden of a specific disorder, families and patients with rare diseases face many of the same challenges, including:

- Lengthy Diagnostic Process: 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 often requires 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 and Emotional: Patients and families often feel alone and isolated in navigating the challenges that accompany diagnosis and treatment of rare diseases.

Despite advances in our understanding of the causes and mechanisms of many rare diseases, effective treatments are available for only a very small number of these conditions—FDA-approved treatments exist for fewer than 5 percent of rare diseases.[1372] 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. As described in more detail below, the RDCRN continues to make progress towards developing treatments and cures for rare diseases.

Scope of NIH Activities: Research and Programmatic

RDCRN.4 consists of 20 consortia (Figure 51) with:

- 170 CPAG partners
- >200 rare diseases being evaluated
- 295 clinical sites across 37 U.S. States
- 10 countries
- Approximately 3,000 researchers and staff

RDCRN

The RDCRN has made outstanding progress over the last 20 years, but it is important to keep pace with changes in science, technology, and the requirements of regulatory agencies and funding sources to ensure continued success in 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 has been 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 lead investigators from each consortium, lead investigators of the DMCC, two CPAG representatives, and NIH program staff. The second is the RDCRN CPAG Steering Committee, with one PAG representative from each consortium, representatives from the DMCC, two lead investigator representatives, and NIH program staff. Each of these two steering committees is led by elected co-chairs,

[1372] https://rarediseases.info.nih.gov/about

who form the third group, the Joint Leadership Committee, which provides oversight for cross-network activities.

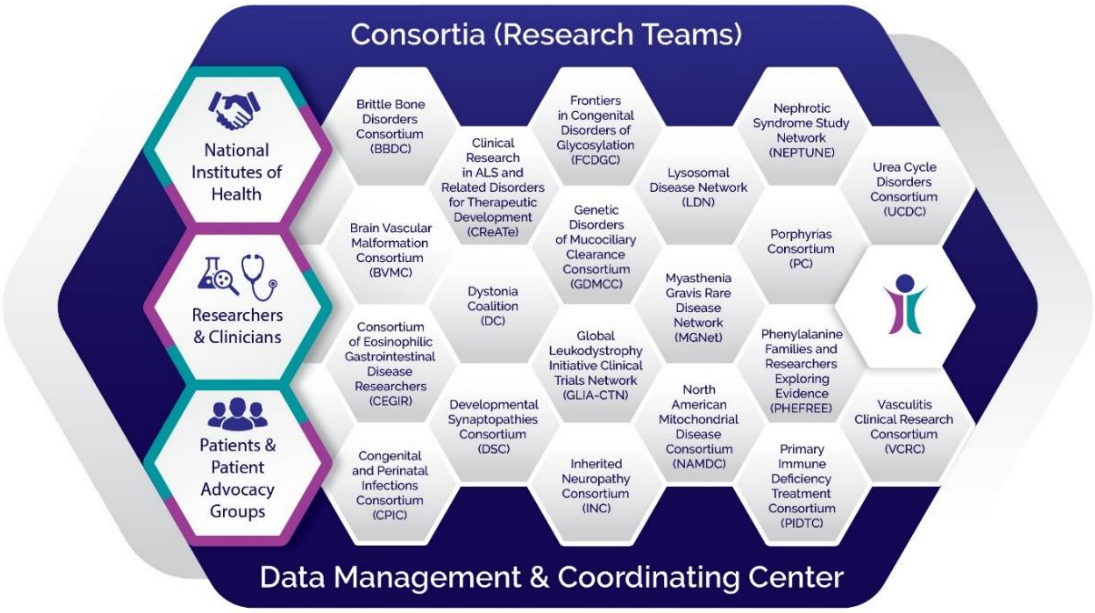


Figure 51: The Rare Disease Clinical Research Network

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. Examples include 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 include studies that validate clinical research tools or develop biomarkers or clinical outcome assessment measures that are fit-for-purpose within a defined context of use relevant to clinical trials. Other consortia studies include projects that expand the knowledge of disease natural history necessary for clinical trial design; studies identifying characteristics for stratification or for determining eligibility criteria for who can participate in the trial; the stage of disease progression that may be responsive to treatment; and data needed to best determine sample sizes necessary to ensure accurate results. 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 centralized support for clinical research and data management to both individual consortia and coordinated activities across the RDCRN. The DMCC also serves as a conduit of information for both the research community and the public, sharing knowledge about 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 Research Core, Engagement and Dissemination Core, and Administrative Core.

The DMCC Data Management Core is responsible for supporting and enhancing a collaborative informatics community for the RDCRN. It does so by focusing on an economies of scale model of shared tools and resources. The flexibility of the DMCC allows it to stay aligned with NIH's Data Management and Sharing Policy as it accomplishes three interrelated tasks. First, the DMCC coordinates and supports efforts to develop and monitor good data practices by promoting findable, accessible, interoperable, and reusable (FAIR) data principles of clinical and research data. It also coordinates and facilitates data standards across the network. Lastly, it encourages the use of common data elements. 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 the REDCap software program 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 Institutional Review Boards (responsible for ensuring human subjects research is conducted responsibly and ethically). Working as collaborative partners, the DMCC Clinical Research Core 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, and 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 rare disease treatments to market. 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 RDCRN.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 lead 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. CPAGs are also vital to the 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 FY22, FY23, and FY24

The RDCRN is made possible through awards by NIH, totaling roughly $33 million in FY24 funding alone, with an average of $1.46 million per consortium per fiscal year. The RDCRN investigators have been able to take advantage of the ripple effect produced by NIH funding, as NIH funding has also attracted the support of CPAGs, industry, angel investors, non-federal grants, and institutional support.

FY22, FY23, and FY24 Progress Report

Programmatic Activities and Outcomes

Examples of some RDCRN programmatic activities and outcomes in FY22, FY23, and FY24 are described below.

- The most recent cycle of the RDCRN has focused on sharing resources across consortia. Centralized shared resources are provided to the network by NIH and managed by the DMCC. This approach is not only prudent but also provides a platform on which network-wide data standards can be established. The standards developed have focused on the FAIR principles, enabling the data to be interoperable with many other existing rare disease data platforms. The network is also in the process of building a secure data-sharing environment managed by NCATS that will provide controlled data access to researchers and the community.
- Between 2003 and 2023, 21 percent of the 3,565 publications produced by the RDCRN were cited in policy documents indexed in Overton, an online, searchable policy citation database, demonstrating the RDCRN's impact on public health policy. The majority of RDCRN citations appear in clinical guidance documents (57 percent), reflecting the network's significant contribution to healthcare practices for rare diseases

Research Activities and Outcomes

Examples of some RDCRN research activities and outcomes in FY22, FY23, and FY24 are outlined below.

- *Kidney tissue atlas provides researchers unprecedented insight into disease.* Developing an effective treatment requires an understanding of the biological components that play a role in a rare disease. RDCRN researchers announced what may be the most comprehensive human kidney cell and tissue catalog to date, the Kidney Tissue Atlas.[1373] Part of the Kidney Precision Medicine Project, the atlas allows researchers to compare healthy kidney cells to injured and diseased cells, providing a framework for the classification of kidney disease. The work promises to provide a better understanding of what leads to kidney disease progression and kidney failure, laying a

[1373] Lake BB, et al. Nature. 2023 Jul;619(7970):585-594. Epub 2023 Jul 19. PMID: 37468583.

foundation for developing new treatments for chronic kidney disease and acute kidney injury. The Atlas represents, in part, a culmination of years of studies on rare kidney disorders, gathered over more than a decade through the RDCRN's Nephrotic Syndrome Study Network. The Atlas data represents 51 kidney cell types and 28 kidney "states" that represent injury or disease and more than 1 million cell "neighborhoods", as well as 3D models of cells and their relationships with their environments. Such studies have provided insights into the molecular details behind kidney diseases.

- *Newborn screening saves lives.* Another RDCRN consortium, the Primary Immune Deficiency Treatment Consortium (PIDTC), made up of 49 collaborating medical centers and seven patient advocacy groups, has written the modern book on severe combined immunodeficiency (SCID). Termed the "bubble boy disease," SCID causes infants to be born without a working immune system, leaving them highly susceptible to infections and with few ways to fight them. Over the last 15 years, the PIDTC has charted the disease's course, developed lifesaving therapies, including gene therapies, and pioneered a newborn screening test. PIDTC scientists revealed what doctors and families already suspected: Newborn screening for SCID saved lives by identifying infants with SCID earlier, leading to faster treatment.[1374] The study examined data on more than 900 children with SCID. PIDTC researchers found that widespread newborn screening for SCID, followed by early treatment, boosted the five-year survival rate of children with the disorder from 73 percent before screening began to 87 percent. Among children whose disease was suspected based on newborn screening rather than on getting sick or family history, 92.5 percent survived five years or more after treatment.

Table 5a. FDA-approved treatments that included RDCRN-related data in the application

Consortium	Drug	Other Name	Indication	Company	Approval Date
UCDC	CARBAGLU®	carglumic acid	N-acetylglutamate synthetase (**NAGS**) deficiency	Orphan Europe	March 2010
VCRC	RITUXAN®	rituximab in combination with corticosteroids	Wegener's granulomatosis (**WG**) and microscopic polyangiitis (**MPA**)	Genentech and Biogen	April 2011
UCDC	RAVICTI®	glycerol phenylbutyrate	urea cycle disorders (**UCD**)	Hyperion Therapeutics	February 2013
RLDC	RAPAMUNE®	sirolimus	lymphangioleiomyomatosis (**LAM**)	Pfizer	May 2015
PC	SCENESSE®	afamelanotide	erythropoietic protoporphyria (**EPP**)	Clinuvel	October 2019
PC	GIVLAARI®	givosiran	acute hepatic porphyria (**AHP**)	Alnylam Pharmaceuticals	November 2019
RKSC	OXLUMO®	lumasiran	primary hyperoxaluria type 1 (**PH1**)	Alnylam Pharmaceuticals	November 2020
CEGIR	DUPIXENT®	dupilumab	eosinophilic esophagitis (**EoE**)	Regeneron	May 2022 Jan 2024 (pediatric)
RTT	DAYBUE™	trofinetide	**Rett** syndrome	Acadia Pharmaceuticals	March 2023
MGNet	RYSTIGGO®	rozanolixizumab-noli	generalized myasthenia gravis (**gMG**)	UCB	June 2023
RKSC	RIVFLOZA™	nedosiran	primary hyperoxaluria type 1 (**PH1**)	Novo Nordisk	October 2023
CEGIR	EOHILIA™	budesonide oral suspension	eosinophilic esophagitis (**EoE**)	Takeda	February 2024

[1374] Thakar MS, et al. Lancet. 2023 Jul 8;402(10396):129-140. Epub 2023 Jun 20. PMID: 37352885.

- *Catalyzing development and approval of new drugs.* Since 2010, 12 treatments for 11 rare diseases have been approved by the FDA, based on clinical trials that utilized RDCRN expertise and infrastructure (Table 5a). Six approvals for five drugs were given during FY22 to FY24 alone.

Recommendations for Improving RDCRNs Effectiveness, Efficiency, and Outcomes

Evaluation Plans

The program will continue to be evaluated by data-driven metrics and NIH programmatic oversite. For example, 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 identified and managed before they become problems.

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 by other rare disease research groups, 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) are scheduled to 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 continue to apply NCATS' approach to translational science that 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 NCATS is taking to transform how research is conducted, to speed the translation of discoveries in the laboratory to therapeutics in the clinic.

In addition, RDCRN.5 will focus on research involving human subjects to plan enrollment for rare disease research studies that will help expand outreach to all rare disease patients. 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.

The DMCC will embrace the NIH Strategic Plan for Data Science[1375] and the NIH Policy for Data Management and Sharing,[1376] with 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.

[1375] https://datascience.nih.gov/nih-strategic-plan-data-science
[1376] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html

Table 4b. All funded RDCRN consortia

Consortium Name	RDCRN.1 2003-2008	RDCRN.2 2009-2013	RDCRN.3 2014-2018	RDCRN.4 2019-2025
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
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			

Consortium Name	RDCRN.1 2003-2008	RDCRN.2 2009-2013	RDCRN.3 2014-2018	RDCRN.4 2019-2025
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

In response to the public health challenges posed by autism spectrum disorder (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. As part of its response to the *Combating Autism Act*, NIH formed the Autism Centers of Excellence (ACE) program by consolidating two previous ASD research programs, the Collaborative Programs of Excellence in Autism (established in 1997) and Studies to Advance Autism Research and Treatment (established in 2002 and completed in 2008), into a single research effort. The *Combating Autism Act* also reauthorized the Interagency Autism Coordinating Committee (IACC)[1377], a federal advisory committee designed to coordinate agency activities and identify priority areas in an annual Strategic Plan for ASD Research, which is used in part to inform the ACE program.

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 and expired in 2024. The *Autism CARES Act of 2019* included new provisions to expand the focus of government activities to include the entire lifespan of people on the autism spectrum. In addition, the Act required a report to Congress on health and well-being. In December 2024, the *Autism CARES Act of 2024* was signed into law (P.L. 118–180), which reauthorizes HHS autism programs through 2029.

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 a majority of NIH's ASD research. The ACC is tasked with enhancing the quality, pace, and coordination of autism research efforts at NIH. 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 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 began in FY07 and was focused on identifying the causes of ASD and developing new

[1377] https://iacc.hhs.gov/

and improved treatments. The second iteration of the ACE program, launched in FY12, focused on possible causes of ASD, risk and resilience in ASD, children with ASD who have limited speech and communication, preventive interventions and improved treatment, ASD among girls and women, and how genetic and environmental factors are associated with the development of ASD. In 2017, the ACE program began its third funding cycle, which addressed the research plan priority areas of research on biomarkers, genetic susceptibility, pharmacological treatments, early intervention, and risk and protective factors. The fourth round of ACE funding began in FY22 and is the focus of the remainder of this section.

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 **Error! Reference source not found.** and the ACE Centers and Networks Active During FY 22 to 24 section below, for more information).

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."[1378] 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. According to CDC's Autism and Developmental Disabilities Monitoring Network,[1379] around 1 in 31 eight-year-old children have autism spectrum disorder (ASD). These estimates are based on data collected from health and special education records of children living

[1378] Kanner L. Nerv Child. 1943;2:217-50.
[1379] https://www.cdc.gov/autism/addm-network/index.html

in 16 areas of the U.S. during 2022. Boys are around three and a half times as likely as girls to be diagnosed with ASD.[1380]

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 expanded criteria to diagnose ASD, or earlier and more accurate ASD diagnoses, or whether it can be attributed to increases in biological, 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 racial, ethnic, and socioeconomic groups and affects every age group. Currently, no coherent and comprehensive system of care is available for affected individuals. People with ASD may receive private and public services in special education settings, hospitals, university medical centers, or residential treatment facilities, among other settings.

The socioeconomic impact of ASD for families and society at large is difficult to accurately estimate, but is believed to be 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. The estimated costs over a lifetime for each person can total $1.4 million to $3 million.[1381,1382,1383] Families often incur large debts for medical and education services that public programs or medical insurance do not cover. In addition, ASD may lead 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, possible environmental risk factors, biomarkers, associations between autism-related genes and physical traits, and potential new interventions to support people with ASD.

To support and accelerate research on the causes, diagnosis, and treatment of ASD, NIH created the National Database for Autism Research, an informatics system and central repository for data from people with ASD. Beginning in 2020, data that were previously stored in the National Database for Autism Research are now incorporated in the NIMH Data Archive.[1384] The archive 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. The NIMH Data Archive provides the infrastructure to store, search across, retrieve, and analyze these varied types of data. Although it receives data from many publicly and privately funded research sources, all ACE centers and networks are expected to contribute their data to the archive.

[1380] Shaw KA. MMWR Surveill Summ 2025;74(No. SS-2):1–22. (https://www.cdc.gov/mmwr/volumes/74/ss/ss7402a1.htm)
[1381] Ganz ML, et al. Arch Pediatr Adolesc Med. 2007;161(4):343-9. PMID: 17404130.
[1382] Buescher AV, et al. JAMA Pediatr. 2014;168(8):721-8. PMID: 24911948.
[1383] Rogge N, et al. J Autism Dev Disord. 2019 Jul;49(7):2873-2900. PMID: 30976961.
[1384] https://nda.nih.gov/

NIH Funding for FY22, FY23, and FY24

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 $23.3 million in FY22, $22.9 million in FY23, and $22.6 million in FY24.

FY22, FY23, and FY24 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, new methods for screening children for early signs of ASD, rare genetic variants and mutations associated with ASD, interactions between environmental exposures and genetic variants to modify autism phenotypes and autism-related outcomes, services for individuals in resource-limited settings, the relationship between sleep disturbances and ASD, emotional and mental health, age-related differences and outcomes, and potential new interventions to support people with ASD. A complete list of the centers and networks that received funding in the first round (FY07 and FY08), second round (FY12 and FY13), third round (FY17 and FY18), and fourth round (FY22 and FY23) are noted in Table 6.

The most recent activities and outcomes of the ACE program in FY22, FY23, and FY24 include:

- *Columbia University Health Sciences (P50HD109879, 2022–2024):* ACE center researchers are comparing the development of a sample of 240 infants at high risk genetically for ASD and other neurodevelopmental conditions to that of a group of 120 infants who do not have a genetic high risk. They are tracking the children's neurological, cognitive, and behavioral development to classify emerging features of ASD in early development, which could then be used to identify other children at risk for ASD. The researchers are also studying the experience of families who have received information about genetic risk, and their choices about early interventions.
- *Stanford University (P50HD109861, 2022–2024):* ACE center scientists are investigating the potential link between ASD and sleep disturbances. Individuals with ASD often have difficulty falling and staying asleep and may awaken frequently during the night. Studies indicate that proper sleep is essential for brain development and function. The research team is monitoring brain waves of people with ASD during sleep and are using other technologies to document their sleep and wake cycles. The scientists hope to determine if unique patterns of sleep disturbances are associated with ASD and whether treating the sleep disturbances will alleviate ASD symptoms.
- *The University of North Carolina at Chapel Hill (R01HD055741, 2007–2024):* ACE network investigators are examining brain and behavior development in a group of 400 children, 300 of whom are at high familial risk of ASD. The children entered this study as infants, before the typical age of onset of ASD, and are now entering adolescence, the time of onset for most adult psychiatric disorders. The researchers are continuing to document the trajectories of brain and behavior development, from infancy through adolescence, in those with ASD as well as those at high risk for ASD who develop other psychiatric conditions that are genetically related to ASD. This study is also focusing on determining the early brain and behavior manifestations of ASD in

females. Females with ASD often present with different symptom patterns and are frequently diagnosed later than males. Understanding brain and behavior trajectories from infancy through adolescence will provide insight relevant to early interventions for ASD and related psychiatric conditions.

- *Drexel University (P50HD111142, 2022–2024):* ACE center researchers are studying ASD among resource-limited individuals to characterize their service use and differences in their health outcomes. Previous studies have shown that resource-limited populations with ASD have less access to healthcare and greater chances for adverse outcomes such as cardiovascular disease and shorter life expectancy. The researchers are studying key stages of the life course: initial diagnosis in childhood, patterns of health and health services use in adolescence and young adulthood, and health and mental health in older adulthood. Results will inform efforts to reduce adverse outcomes and promote wellbeing for people with ASD.
- *Duke University (P50HD093074, 2017–2024):* ACE center scientists are developing new methods to screen children for early signs of autism. They are studying a digital app that is used at home on smart phones and tablets to videotape young children's behavior and interactions with their caregivers. Super intelligence and computer vision automatically codes the videotapes to identify behavioral characteristics of children who are later diagnosed with autism and their long-term development tracked. They are also using SI to analyze health insurance claims and medical records for roughly 230,000 children (about 6,000 with ASD) from birth to 18 months to develop an algorithm to predict later ASD during infancy and identify the nature and prevalence of early medical conditions associated with later diagnosis of ASD. Based on the algorithm, they are developing automated decision support for primary care providers. The research team are also using SI to analyze electroencephalograms (brain wave activity), which are synchronized with videotaped behavior of 3- to 6-year-old children to identify brain activity associated with accompanying behaviors characteristic of ASD.
- *University of Wisconsin-Madison (R01MH132218, 2022–2024):* ACE network investigators are overseeing a project that follows autistic adults as they age. Recent studies suggest that older adults with ASD may have shorter life expectancies and more physical and mental health difficulties than the general population. The project is enrolling a large group of adults with and without ASD. The researchers are using a broad range of measures to study changes in the participants' well-being, physical and mental health, and brain structure and function. The goal is to examine how aging-related differences may contribute to different outcomes, including decline and resilience, to improve the long-term health of autistic adults.
- *University of Pittsburgh (P50MH130957, 2022–2024):* ACE center researchers are investigating emotional and mental health in autistic adults, a population that has a potentially higher risk for suicide. Together with autistic adults and community partners, the researchers are using a longitudinal, multimethod approach that integrates clinical and behavioral measures, neuroimaging, and self-report of experiences linked with physiological responses. With these measures, the research team is examining predictors of suicide ideation and behaviors at the group and individual level and validating a suicide risk self-report measure. The investigators also are considering various factors that may play a role in mental health outcomes, such as age of

autism diagnosis, sex, mental health diagnoses, and trauma history. The overall goal of this project is to generate information needed to improve autistic adults' mental health and quality of life and reduce their risk of premature mortality.

- *University of Virginia (R01MH100028, 2012–2024):* ACE network scientists aim to develop effective methods for identifying older autistic adolescents and adults who are often misdiagnosed, diagnosed late, or not diagnosed at all. Late diagnosis, misdiagnosis, or lack of diagnosis puts individuals with ASD at greater risk for depression, anxiety, and self-harm and can negatively impact their quality of life. Using brain and behavioral measures, the researchers are focusing on understanding predictors of late diagnosis and on developing a new autism screening tool to identify individuals at risk for late diagnosis. The goal is to help autistic adolescents and adults receive timely and appropriate services and supports to improve overall outcomes.
- *Johns Hopkins University (R01ES034554, 2022–2024):* ACE network investigators aim to understand how genetic and environmental factors interact to affect ASD and health outcomes. The research team is coordinating and evaluating data from ongoing population studies that include 175,000 individuals to determine how environmental factors such as air pollution, prenatal maternal infection, and prenatal nutrition influence the risk for ASD and the symptom severity accompanying genetic variants associated with ASD. The researchers are also developing and implementing an outreach and dissemination strategy for new findings.
- *University of California, Los Angeles (R01MH100027, 2013–2024):* ACE network researchers 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,[1385] common inherited variants or mutations at the family level exert stronger effects on ASD risk.[1386] These researchers also reported that in families with multiple affected individuals, a substantial contribution to ASD risk comes from inherited rare variations.[1387] In the current funding cycle, these scientists aim to further explore the genetics of autism by increasing the size of this cohort.
- *University of California, Los Angeles (P50HD055784, 2007–2024):* For more than a decade, scientists at this 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. These scientists continue to work to determine how differences in genetic risk for autism affect early brain development, neuroimaging, and electroencephalogram (measures electrical activity in the brain) biomarkers in the first year of life. They plan to examine differences in treatment response using an adaptive treatment

[1385] Anney R, et al. Hum Mol Genet. 2012;21(21):4781-92. PMID: 22843504.
[1386] Gaugler T, et al. Nat Genet. 2014;46(8):881-5. PMID: 25038753.
[1387] Leppa VM, et al. Am J Hum Genet. 2016;99(3):540 PMID: 27569545.

intervention for very young children at risk for ASD, to use MRI to determine how behavioral differences and genetic risk differentially affect brain activation and structural and functional connectivity in youth with ASD, and to conduct an early-stage pharmacological study aimed to increase social interest and social reward responsivity in adolescents and young adults.

- *Florida State University (R01HD093055, 2017–2023):* ACE network researchers tested a two-part intervention designed to empower parents of children with ASD. The researchers offered 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 received training in early social interaction, which taught them to support their children's communication and social skills in everyday routines, activities, and settings.
- *University of California, Davis (P50HD093079, 2017–2023):* ACE center scientists classified children into different subgroups of ASD, based on their symptoms, behavioral characteristics, and genetic features. The researchers found that by age three, about 15 percent of boys with ASD had brains that were disproportionately large relative to the size of their bodies. These boys had a higher rate of regression, or loss of social and communications skills, and were more likely to have an intellectual disability. In contrast, at age three, only three percent of girls with ASD had disproportionately large brains. The scientists are following these children through childhood to determine whether the structure of their brains differed from those of typically developing children.
- *Yale University (P50MH115716, 2017–2023):* ACE center scientists examined whether boys and girls with ASD differ in their brain circuitry, with the aim of improving diagnosis and treatment. In addition, they evaluated an intervention to improve social functioning in children at high risk for ASD. Scientists also investigated brain connections in fetuses and newborns to identify early indicators of ASD.[1388] They found that differences in network asymmetries associated with ASD risk are observable prior to the age of a reliable clinical diagnosis.

Recommendations for Improving ACE Programs Effectiveness, Efficiency, and Outcomes

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, staff at the five NIH Institutes (NICHD, NIDCD, NIEHS, NIMH, and NINDS) that provide financial support and scientific expertise to the ACE program gathered data to assess the implementation and outputs of the ACE program from 2010 through 2014. This included an evaluation of research, training, and dissemination activities of the ACE centers and networks, as well as research collaborations and community partnerships.

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 also building research capacity in the field by training postdoctoral and early-

[1388] Rolison M, et al. Cereb Cortex. 2022 Mar 4;32(6):1212-1222. PMID: 34424949.

career researchers. Data from this program have been shared with the research community through several available databases, including the NIMH Data Archive, Autism Brain Imaging Data Exchange, Marcus Autism Center Vocal, Autism Speaks Baby Sibs Research Consortium, Autism Genetic Research Exchange, NIMH Repository and Genomics Resource, and molecular data repositories managed and maintained by the NLM's National Center for Biotechnology Information, which hosts genetic and gene expression data. Scientific findings have been disseminated across numerous venues and forums, including grant recipient 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

With the enactment of the *Autism CARES Act of 2024* (P.L. 118–180), NIH will continue efforts related to the expansion, intensification, and coordination of autism research activities, including the ACE program. For example, NIH has convened an annual, two-day meeting during which investigators present progress toward the goals of their ACE and exchange ideas for collaborations. ACE lead investigators, project investigators, core directors, and data managers all attend. Investigators are encouraged to invite career development grant recipients, fellows, and postdoctoral students from their respective laboratories to learn about research advances and future directions of the ACE program.

Table 5. Autism Centers of Excellence (ACEs)

Institution and Location	Year 1st Round Started	Year 2nd Round Started	Year 3rd Round Started	Year 4th Round Started
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	2023
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	2022
The University of North Carolina, Chapel Hill, NC (2)	—	2012	—	—
University of Pittsburgh, Pittsburgh, PA (1)	2007	—	—	—
University of Pittsburgh, Pittsburgh, PA (2)	—	—	—	2022
University of Washington, Seattle, WA	2007	—	—	—
Yale University, New Haven, CT	2008	2012	2017	—
Wayne State University, Detroit, MI	2008	—	—	—
Drexel University, Philadelphia, PA (1)	2008	—	—	—
Drexel University, Philadelphia, PA (2)	—	—	2017	—
Drexel University, Philadelphia, PA (3)	—	—	—	2022
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	—	—

Institution and Location	Year 1st Round Started	Year 2nd Round Started	Year 3rd Round Started	Year 4th Round Started
Duke University, Durham, NC	—	—	2017	2022
Florida State University, Tallahassee, FL	—	—	2017	—
The George Washington University, Washington, DC	—	—	2017*	—
The University of Virginia, Charlottesville, VA	—	—	2018*	2022
Columbia University Health Sciences, New York City, NY	—	—	—	2022
Stanford University, Stanford, CA	—	—	—	2022
The University of Wisconsin-Madison, Madison, WI	—	—	—	2022
Johns Hopkins University, Baltimore, MD	—	—	—	2022

*Funding for the R01MH100028 ACE network was transferred from George Washington University, Washington, DC, to University of Virginia, Charlottesville, VA, in 2018 when the Principal Investigator moved institutions.

Appendix A: Excerpts of Legal Authorities Related to the NIH Director's Triennial Report to Congress

PUBLIC HEALTH SERVICE ACT

APPOINTMENT AND AUTHORITY OF DIRECTOR OF NIH

SECTION 402(b) In carrying out the purposes of section 301, the Secretary, acting through the Director of NIH—(7)(A) shall, through the Division of Program Coordination, Planning, and Strategic Initiatives—(ii) include information on such research in reports under section 403.

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TRANS-NIH RESEARCH REPORTING

SECTION 402A(c)(2)(B) REPORTING.—Not later than 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.

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TRIENNIAL REPORTS OF DIRECTOR OF NIH

SECTION 403(a) IN GENERAL.—The Director of NIH shall submit to the Congress on a triennial basis a report in accordance with this section. The first report shall be submitted not later than 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.

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SCIENTIFIC FRAMEWORK FOR RECALCITRANT CANCERS

SECTION 417G

(d) REPORTING.—

(1) BIENNIAL REPORTS.—The Director of NIH shall ensure each biennial[1389] report under section 403 includes information on actions undertaken to carry out each scientific framework developed under subsection (a) with respect to a recalcitrant cancer, including the following:
    (A) Information on research grants awarded by the National Institutes of Health for research relating to such cancer.
    (B) An assessment of the progress made in improving outcomes (including relative survival rates) for individuals diagnosed with such cancer.
    (C) An update on activities pertaining to such cancer under the authority of section 413(b)(7).

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OFFICE OF RESEARCH ON WOMEN'S HEALTH

SECTION 486(d)(5) ADVISORY COMMITTEE.—

(A) The Advisory Committee shall prepare a biennial report describing the activities of the Committee, including findings made by the Committee regarding—
    (i) compliance with section 492B;

[1389] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

(ii) the extent of expenditures made for research on women's health by the agencies of the National Institutes of Health; and
(iii) the level of funding needed for such research.

(B) The report required in subparagraph (A) shall be submitted to the Director of NIH for inclusion in the report required in section 403.

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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[1390] REPORT OF DIRECTOR OF NIH.—The Director of the Office shall submit each report prepared under subsection (a) to the Director of NIH for inclusion in the report submitted to the President and the Congress under section 403.

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INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

SECTION 492B(f) REPORTS BY ADVISORY COUNCILS.—The advisory council of each national research institute shall prepare triennial reports describing the manner in which the institute has complied with this section. Each such report shall be submitted to the Director of the institute involved for inclusion in the triennial report under section 403.

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HUNTER KELLY RESEARCH PROGRAM

SECTION 1116(c) REPORTS.—The Director is encouraged to include information about the activities carried out under this section in the biennial[1391] report required under section 403. If such information is

[1390] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.
[1391] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

included, the Director shall make such information available to be included on the Internet Clearinghouse established under section 1112.

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MICROBICIDE RESEARCH

SECTION 2351A(a) FEDERAL STRATEGIC PLAN.—The Director of the Office shall—

(1) expedite the implementation of the Federal strategic plans required by section 403(a) of the *Public Health Service Act* (42 U.S.C. 283(a)(5)) regarding the conduct and support of research on, and development of, a microbicide to prevent the transmission of the human immunodeficiency virus; and
(2) review and, as appropriate, revise such plan to prioritize funding and activities relative to their scientific urgency and potential market readiness.

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(b) TRACKING; REPORTING.—The Director of the National Institutes of Health shall—

(1) collect information on—

(A) the effect of innovations funded through the prize competitions under this section in advancing biomedical science or improving health outcomes pursuant to subsection (a); and

(B) the effect of the innovations on Federal expenditures; and

(2) include the information collected under paragraph (1) in the triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032).

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APPROPRIATE AGE GROUPINGS IN CLINICAL RESEARCH

SECTION 2038(i)(3) PUBLIC AVAILABILITY OF FINDINGS AND CONCLUSIONS.—The Director of the National Institutes of Health shall –

(A) make the findings and conclusions resulting from the workshop under paragraph (1) and updates to policies in accordance with paragraph (2), as applicable, available to the public on the Internet website of the National Institutes of Health; and

(B) ensure that age-related data reported in the triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032) are made available to the public on the Internet website of the National Institutes of Health.

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TICK-BORNE DISEASES

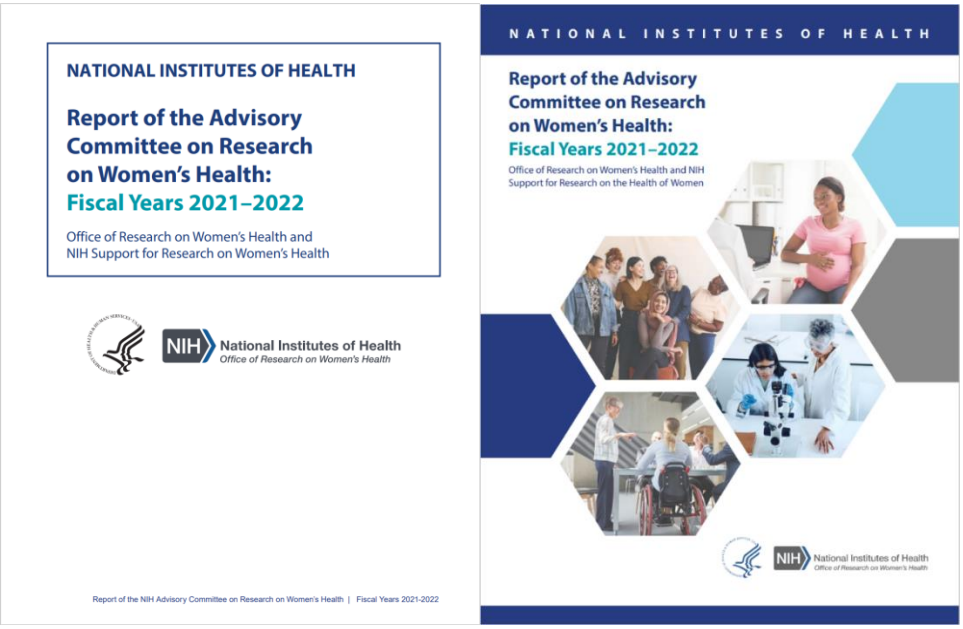
SECTION 2062(a) IN GENERAL.—The Secretary of Health and Human Services (referred to in this section as ‘‘the Secretary’’) shall continue to conduct or support epidemiological, basic, translational, and clinical research related to vector-borne diseases, including tick-borne diseases.

(b) REPORTS.—The Secretary shall ensure that each triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032) includes information on actions undertaken by the National Institutes of Health to carry out subsection (a) with respect to tick-borne diseases.

Appendix B: Report of the Advisory Committee on Research on Women's Health

This report details the NIH-wide programs and accomplishments carried out in fulfillment of the core mission of the NIH Office of Research on Women's Health.[1393] The report also provides highlights from research on women's health and on the influence of sex on health and disease supported by NIH ICOs. New to the report for FY21 and FY22 is the section titled ICOs' Crosscutting Integrative Topics in Research on the Health of Women. This section details ICO collaborative efforts on crosscutting areas related to the health of women and highlights examples of programs in those areas. These efforts are aimed at bridging research gaps, enhancing the impact of research support, and offering novel approaches to accelerate biomedical advances that improve health outcomes for all women. In addition, the report presents ORWH co-funding with the ICs in targeted research activities, such as pain research and maternal morbidity and mortality. It also includes research dissemination and engagement activities and data on NIH grant funding and success rates by sex during FY16 to FY22. Finally, the report documents the inclusion of women and minorities as participants in NIH-funded clinical research during these years, as required by law.[1394]

For the full report, please see:
https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Biennial%20Report_121823_1516_F_508c_Optimized.pdf



[1393] https://orwh.od.nih.gov/
[1394] https://grants.nih.gov/policy-and-compliance/policy-topics/inclusion/women-and-minorities

Appendix C: Actions Undertaken to Conduct or Support Research Related to Vector-Borne Diseases

NIH conducts and supports extensive research to advance science and develop methods to prevent, diagnose, and treat vector-borne diseases (VBDs), as well as control the vectors that spread these diseases to humans. From FY22 to FY24, NIH allocated $828 million, $746 million, and $737 million, respectively, for this research.[1395] In compliance with the *21st Century Cures Act* (P.L. 114-255), NIH has prepared this report on epidemiological, fundamental, translational, and clinical research related to VBDs, including tick-borne diseases (TBDs).[1396] This report offers a representative overview of NIH-supported and -conducted research in this field. For a detailed list of VBD research activities at NIH, visit the NIH Research Portfolio Online Reporting Tools (RePORT) website.[1397]

Background

Arthropod vectors, such as certain insects and ticks, can transmit numerous infectious disease pathogens to humans, posing a significant public health threat. According to the World Health Organization,[1398] VBDs account for more than 17 percent of all infectious diseases worldwide, causing more than 700,000 deaths annually. In the past decade, outbreaks of mosquito-borne viruses like Dengue, Zika, and Chikungunya in the Americas highlight the critical need for ongoing research and development to effectively combat these emerging infectious diseases.

Since 2004, cases of VBDs have surged in the U.S., with more than a million reported by 2023. However, the actual numbers may be significantly higher due to underreporting.[1399] The CDC has published the *National Public Health Strategy to Prevent and Control Vector-Borne Diseases in People*[1400] to address the rising public health threat of VBD. This rise in VBD incidence represents a growing public health threat, driven by emerging pathogens and changing geographic distributions of vectors influenced by factors such as land use, socioeconomic conditions, and climate shifts. Specifically, tick-borne diseases, including Lyme disease, anaplasmosis, babesiosis, and others, are increasingly threatening health as vector ranges expand, with Lyme disease being the most common VBD in the U.S.

Unlike infectious diseases that spread directly from person to person or through intermediate surface contact, VBDs are transmitted through a complex interplay of human hosts, pathogens, insect 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.

[1395] https://report.nih.gov/funding/categorical-spending#/
[1396] 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.
[1397] https://report.nih.gov/funding/categorical-spending#/
[1398] https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases
[1399] https://www.cdc.gov/vector-borne-diseases/about/index.html
[1400] https://www.cdc.gov/vector-borne-diseases/php/data-research/national-strategy/index.html

NIH supports research to understand the impact of vector-borne pathogen 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, examination 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 candidates and therapeutics for VBDs.

NIH also continues to support epidemiological, 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 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 Actions to Support Vector-Borne Disease Research

Research Updates

Chikungunya

Chikungunya virus (CHIKV)[1401] is a member of the alphavirus genus and is transmitted to people via the bite of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes, both of which have geographic ranges that include large parts of the continental U.S.[1402] Viral reservoirs include humans, rodents, birds, monkeys, and other animals. CHIKV was discovered in Tanzania in 1952; and since 2013, CHIKV has spread rapidly into parts of Europe, the Caribbean Islands, and Central and South America. Local transmission of CHIKV was identified in Florida, Texas, Puerto Rico, and the U.S. Virgin Islands beginning in 2014; however, since 2019 no locally acquired cases have been reported from U.S. states or territories.[1403] Chikungunya disease is a severe, debilitating, febrile, arthritic disease. Severe neonatal infection can occur at birth if the mother is infected with CHIKV. During the FY22 to FY24 reporting period, no licensed vaccines or therapeutics existed for this disease. Below are select chikungunya research advances and highlights for FY22 to FY24.

Epidemiological Research

- Worked to disentangle the human-vector relationship of Dengue and chikungunya in Kenya. (NIAID; R01AI102918)
- Traced the evolution of CHIKV and analyzed CHIKV epidemics and transmission.[1404,1405,1406,1407,1408] (NIAID)
- Investigated the percentage of people in a population who test seropositive for CHIKV.[1409] (NIAID)

[1401] https://www.cdc.gov/chikungunya/about/index.html
[1402] https://www.cdc.gov/mosquitoes/php/toolkit/potential-range-of-aedes.html
[1403] https://www.cdc.gov/chikungunya/data-maps/chikungunya-us.html
[1404] Argibay HD, et al. Lancet Reg Health Am. 2025 Jan 24;43:101003. PMID: 39925861.
[1405] Dieng I, et al. Emerg Microbes Infect. 2024 Dec;13(1):2373308. Epub 2024 Jul 22. PMID: 38934257.
[1406] Burgueño A, et al. Emerg Microbes Infect. 2024 Dec;13(1):2332672. Epub 2024 Apr 15. PMID: 38517841.
[1407] Ramphal Y, et al. Pathogens. 2024 Jul 22;13(7):605. PMID: 39057831.
[1408] Fabbri C, et al. Emerg Microbes Infect. 2024 Dec;13(1):2362941. Epub 2024 Jun 10. PMID: 38813649.
[1409] Allen SW, et al. J Infect Dis. 2024 Nov 15;230(5):e1031-e1038. PMID: 38942731.

- Unraveled immunological and genetic insights in CHIKV infection.[1410] (NIAID)

Fundamental Research

- Worked to define mechanisms of protection, pathogenesis, and immunity during viral infection, with a focus on alphaviruses, including CHIKV. (NIAID)
- Invested in the establishment and characterization of a new mouse model to study the neuropathogenesis and long-term neurological effects of CHIKV infection. (NINDS; R21NS135258)
- Investigated the relationship between gut microbiota and CHIKV by:
    - Defining how the gut microbiota modulates CHIKV infection, dissemination, and musculoskeletal disease. (NIAID; R01AI152484)
    - Understanding the role of gut microbiota in modulating antiviral immune responses of plasmacytoid dendritic immune cells to CHIKV. (NIAID; F30AI152327)
- Studied B and T immune cell discovery and responses to CHIKV by:
    - Identifying human B cell epitopes (the part of the virus that is recognized by the immune system) of CHIKV to understand protective immunity mediated by antibodies as well as pathological consequences of antibody responses. (NIAID)
    - Discovering global identification of epitopes derived from Zika and CHIKV following natural infection and vaccination in humans. (NIAID)
    - Defining mechanistically how pathogenic CHIKV evades B cell-mediated clearance to establish persistent infection. (NIAID; R01AI141436)

Translational Research

- Evaluated vaccine strategies for Zika, Chikungunya, Dengue, Leishmania, Malaria, and other important or emerging VBDs. (NIAID; ZIAAI001221)
- Sought to enhance the therapeutic activity of CHIKV hyperimmune IgG antibodies, which are antibodies isolated from donors with high antibody levels against CHIKV that provide immediate, short-term immunity.[1411] (NIAID)
- Investigated an experimental antiviral compound designed to reduce viral load. (NIAID)
- Focused on eliciting neutralizing antibody against CHIKV in mice.[1412] (NIAID)

Clinical Research

- Conducted a Phase 1 clinical trial for a therapeutic monoclonal antibody for CHIKV. (NIAID; NCT04441905)
- Demonstrated that an experimental chikungunya vaccine, PXVX0317, elicited a strong and lasting antibody response against CHIKV.[1413] (NIAID)
- Assessed a novel, inactivated CHIKV vaccine (HydroVax-CHIKV) in a randomized Phase 1 clinical trial. (NIAID; U44AI152995)

Dengue Fever

[1410] Fritsch H, et al. Genes (Basel). 2024 Oct 24;15(11):1365. PMID: 39596565.
[1411] Fox JM, et al. Front Immunol. 2023 May 12;14:1153108. PMID: 37251375.
[1412] Tong K, et al. Vaccine. 2024 Dec 2;42(26):126405. Epub 2024 Oct 15. PMID: 39413488.
[1413] Raju S, et al. Sci Transl Med. 2023 May 17;15(696):eade8273. Epub 2023 May 17. PMID: 37196061.

Dengue fever, a common mosquito-borne viral disease, occurs in most tropical and subtropical regions of the world.[1414] Dengue fever is caused by four distinct variations (serotypes) of Dengue virus (DENV), a flavivirus transmitted to humans by *A. aegypti* and *A. albopictus* mosquitoes, which are found in the U.S., and thrive in urban and semiurban environments. Most dengue cases reported in the 49 continental U.S. states occur in travelers infected elsewhere; however, local transmission occasionally occurs and has been identified in California, Florida, Hawaii, Arizonia, and Texas.[1415] 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. In addition to the acute symptoms, some people develop longer-lasting post-acute Dengue disability. Below are select dengue fever research advances and highlights for FY22 to FY24.

Epidemiological Research

- Investigated previous exposure to DENV as a risk factor for Zika during pregnancy. (NIAID; R01AI132563)
- Assessed immunity from Zika infection and its effect on DENV immunity.[1416,1417] (NIAID)
- Studied simultaneous co-circulation of multiple DENV serotypes causing outbreaks.[1418,1419] (NIAID)
- Explored DENV infection and diabetes comorbidity as an emerging public health threat.[1420] (NIAID)

Fundamental Research

- Investigated mechanisms of antibody-dependent enhancement of Dengue disease. (NIAID; R01AI137276)
- Analyzed serological markers of protection and protective immunity of Dengue vaccines and natural infection. (NIAID; R01AI175495 and P01AI106695)
- Aimed to phenotype human immune responses to Dengue natural infection, vaccination, and challenge. (NIAID; U19AI168631)
- Showed that effectiveness of neutralizing antibodies in fighting DENV can vary significantly based on prior infection history and infecting serotype.[1421] (NIAID)
- Established that a live DENV vaccine carrying a combination of proteins from two DENV serotypes elicits dual immunity against both serotypes.[1422] (NIAID)

Translational Research

- Evaluated therapeutics and vaccines in mouse models of DENV. (NIAID)
- Advanced development of flavivirus and alphavirus vaccine platforms. (NIAID; U19AI181960)

[1414] https://www.who.int/news-room/fact-sheets/detail/Dengue-and-severe-Dengue
[1415] https://www.cdc.gov/dengue/data-research/facts-stats/index.html
[1416] Aogo RA, et al. Sci Transl Med. 2023 Nov 15;15(722):eadi1734. Epub 2023 Nov 15. PMID: 37967199.
[1417] Zambrana JV, et al. Sci Transl Med. 2024 May 29;16(749):eadn2199. Epub 2024 May 29. PMID: 38809964.
[1418] Ariyaratne D, et al. J Infect Dis. 2025 Apr 15;231(4):1041-1048. PMID: 39387651.
[1419] van der Ende J, et al. Emerg Infect Dis. 2025 Jan;31(1):202-204. Epub 2024 Dec 11. PMID: 39662875.
[1420] Bisanzio D, et al. Int Health. 2024 Dec 16:ihae089. Epub ahead of print. PMID: 39676570.
[1421] Bos S, et al. Nat Commun. 2024 Jan 9;15(1):382. PMID: 38195666.
[1422] Young E, et al. Nat Commun. 2023 Mar 13;14(1):1371. PMID: 36914616.

- Advanced a rapid point-of-care RNA diagnostic for Dengue infection; and a single point-of-care test for simultaneous diagnosis of Dengue and prognosis of severe Dengue. (NIAID; R44AI140813 and R43AI162484)
- Integrated three high-throughput systems biology approaches to identify critical host proteins and pathways for DENV replication.[1423] (NIAID)
- Applied molecular approaches to define how vaccine-induced development of Dengue-specific immunity safely and durably protects against infection and disease. (NIAID; U01AI141997)
- Investigated the Dengue epidemic dynamics of boosting and waning in highly exposed populations.[1424] (NIAID)

Clinical Research

- Evaluated TetraVax-DV, a live weakened Dengue vaccine, in a Dengue endemic population and conducted a Phase 3 clinical trial of TetraVax-DV in Brazil.[1425,1426] (NIAID; U01AI134582)
- Showed that obesity is associated with increased susceptibility to DENV infection and dengue cases in children.[1427] (NIAID)

Lyme Disease and Other Tickborne Diseases

Ticks can transmit a variety of disease-causing pathogens, including those responsible for Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, babesiosis, severe fever with thrombocytopenia syndrome, and Powassan disease.[1428] Lyme disease, the most prevalent of the tick-transmitted infections in the U.S., is caused by the bacterium *Borrelia burgdorferi*.[1429] Over 89,000 cases of Lyme disease were reported in 2023; however, this may represent an underestimate. Estimates using other methods suggest that up to 476,000 people may be diagnosed and treated for Lyme disease each year. This number likely includes patients who are treated based on clinical suspicion but do not actually have Lyme disease.[1430]

Symptoms of Lyme disease include 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. Some PTLDS patients develop autoimmune diseases including arthritis, lupus, polymyalgia rheumatica, thyroid disease, and autoimmune neuropathy. It remains unclear whether the features of Lyme disease simply mimic these autoimmune conditions or if Lyme disease triggers autoimmunity leading to these disease manifestations.

Powassan virus is also spread to people by the bite of an infected tick and although still rare (around 40 cases per year), the number of reported cases has increased in recent years.[1431] Most cases in the U.S. occur in the northeast and Great Lakes regions. Initial symptoms can include fever, headache, vomiting,

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[1423] Song G, et al. Genomics Proteomics Bioinformatics. 2022 Aug;20(4):808-809. Erratum for: Genomics Proteomics Bioinformatics. 2021 Feb;19(1):108-122. PMID: 36669818.
[1424] Aogo RA, et al. Sci Transl Med. 2023 Nov 15;15(722):eadi1734. Epub 2023 Nov 15. PMID: 37967199.
[1425] Kallás EG, et al. N Engl J Med. 2024 Feb 1;390(5):397-408. PMID: 38294972.
[1426] Nogueira ML, et al. Lancet Infect Dis. 2024 Nov;24(11):1234-1244. Epub 2024 Aug 5. PMID: 39116904.
[1427] Mercado-Hernandez R, et al. Clin Infect Dis. 2024 Oct 15;79(4):1102-1108. PMID: 39004909.
[1428] https://www.cdc.gov/ticks/about/
[1429] https://www.cdc.gov/lyme/about/index.html
[1430] https://www.cdc.gov/lyme/data-research/facts-stats/index.html
[1431] https://www.cdc.gov/powassan/data-maps/historic-data.html

and weakness. Powassan virus can cause severe disease, including inflammation of the brain (encephalitis) or the membranes around the brain and spinal cord (meningitis). Symptoms of severe disease include confusion, loss of coordination, difficulty speaking, and seizures.[1432]

Over the past decade, information has emerged about alpha-gal syndrome (AGS)[1433]—a unique food allergy to a sugar (galactose-a-1,3-galactose or alpha-Gal) present in non-primate mammalian meat. There is evidence that AGS in the U.S. is associated with tick bites, particularly by the lone star tick, but it is not clear how tick bites lead to AGS. People who suffer from AGS develop reactions within 2 to 6 hours after consuming mammalian meat ranging from gastrointestinal symptoms to generalized hives and life-threatening systemic allergic reactions (anaphylaxis).

Current strategies to address TBDs are hindered by suboptimal diagnostics, few treatment options, a lack of vaccines, and ineffective tick control approaches. In 2019, the NIH published the *NIH Strategic Plan for Tick-borne Disease Research*,[1434] 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. Progress made since then to advance Lyme disease and other TBDs research is highlighted below.

Epidemiological Research

- Investigated prevalence of tick infestation and insights into tick vectors of Crimean-Congo Hemorrhagic Fever Virus.[1435,1436,1437] (NIAID)
- Identified Bourbon Virus neutralizing antibodies in wildlife in Missouri, and evidence of infection in humans in North Carolina.[1438,1439] (NIAID)
- Measured alpha-gal IgE antibodies (important for immune response to certain infections and in various allergic diseases) in participants of the 2025-2026 National Health and Nutrition Examination Survey conducted by the CDC. (NIAID)
- Addressed the emergence of AGS by investigating its mechanisms, characterizing its epidemiology, and developing diagnostics and therapies. (NIAID)

Fundamental Research

- Characterized the fundamental biological principles of pathogenic spirochetes (class of bacteria that includes *B. burgdorferi*) and the molecular mechanisms that regulate their infectivity. (NIAID)
- Sought to map the boundaries of all RNA transcripts in *B. burgdorferi*.[1440] (NICHD, NIAID)
- Identified human antibodies that neutralize tick-borne flaviviruses.[1441] (NIAID)
- Advanced understanding of post treatment Lyme disease syndrome by:

[1432] https://www.cdc.gov/powassan/data-maps/index.html
[1433] https://www.cdc.gov/alpha-gal-syndrome/about/index.html
[1434] https://www.niaid.nih.gov/sites/default/files/NIH-Strategic-Plan-Tickborne-Disease-Research-2019.pdf
[1435] Khoule A, et al. Vet Med Sci. 2025 May;11(3):e70165. PMID: 40159441.
[1436] Bratuleanu BE, et al. Parasit Vectors. 2024 Nov 22;17(1):482. PMID: 39578881.
[1437] Ngom D, et al. Zoonoses Public Health. 2024 Sep;71(6):696-707. Epub 2024 Apr 16. PMID: 38627964.
[1438] Bamunuarachchi G, et al. Vector Borne Zoonotic Dis. 2025 Apr;25(4):287-294. Epub 2025 Feb 14. PMID: 39950953.
[1439] Zychowski DL, et al. Emerg Infect Dis. 2024 Nov;30(11):2396-2399. Epub 2024 Oct 9. PMID: 39387510.
[1440] Petroni E, et al. Nat Commun. 2023 Jul 4;14(1):3931. PMID: 37402717.
[1441] Cervantes Rincón T, et al. Cell Rep. 2024 Jun 25;43(6):114298. Epub 2024 May 29. PMID: 38819991.

    - Evaluating how the natural release of unusual peptidoglycan (component of bacteria cell wall) fragments drives persistent Lyme disease symptoms. (NIAID; R01AI178711)
    - Investigating novel immune biomarkers to predict Lyme disease progression and recovery. (NIAID; R01AI178713)
    - Studying clinical, immunologic, and metabolic determinants of PTLDS; including the role of auto-antibodies as predictive markers. (NIAID; R01AI178726 and R01AI178725)
    - Discovering early immunologic biomarkers for risk of PTLDS through machine learning-assisted profiling of humoral immune response (aspect of immunity mediated by secreted molecules, including the antibody response). (NIAID; R01AI178727)
    - Investigating the neurocognitive symptoms associated with PTLDS. (NIAID; R01AI178774)
- Assessed pathogen colonization and immune avoidance by spirochetes by:
    - Understanding immune evasion and persistence by *B. burgdorferi* and other Lyme disease-causing *Borrelia* species. (NIAID; R21AI148701)
    - Evaluating the role of linear plasmid 17 in host colonization by *B. burgdorferi*. (NIAID; R21AI155756 and R21AI158947)
    - Understanding how infection by *B. burgdorferi* establishes disease of the central nervous system. (NIAID; R01AI158304)
    - Identifying the targets of antibodies that are produced in the skin lesion erythema migrans, a clinical sign of early Lyme disease. (NIAID; R21AI153644)
- Assessed host heterogeneity and its effects on susceptibility to *Babesia microti* infection, the bacteria that causes babesiosis. (NIAID; R21AI185273)
- Examined the structural and functional alteration of red blood cells by *B. microti*. (NIAID; K99AI182422)
- Investigated B cell epitopes and mechanisms of antibody protection in Crimean-Congo and Powassan viruses and *Borrelia* species. (NIAID; R44AI157650)
- Demonstrated that blacklegged ticks are susceptible to, and capable of transmitting, Powassan virus.[1442] (NIAID)
- Showed that viral genomic data from Powassan virus human infections typify the variability of genome sequences seen in ticks.[1443] (NIAID)
- Provided evidence that age-dependent Powassan virus lethality is linked to glial cell activation and divergent neuroinflammatory cytokine responses in a mouse model.[1444] (NIAID)

Translational Research

- Developing and miniaturizing a high-throughput assay for *B. burgdorferi* infection. (NCATS; ZIATR000355, ZIATR000412, and ZIATR000413)
- Advanced diagnostic assays for Lyme disease by:
    - Investigating a multi-antigen point-of-care assay that will provide immediate detection of antibodies against *B. burgdorferi* (an antigen is a substance recognized by the immune system that triggers an immune response). (NIAID; R44AI150060)
    - Investigating a highly-sensitive, rapid, and low cost plasmonic assay platform (miniaturized optical devices) for Lyme disease diagnosis. (NIAID; R41AI167161)

[1442] McMinn RJ, et al. Viruses. 2024 May 23;16(6):830. PMID: 38932123.

[1443] Klontz EH, et al. Viruses. 2024 Oct 23;16(11):1653. PMID: 39599768.

[1444] Mladinich MC, et al. J Virol. 2024 Aug 20;98(8):e0056024. Epub 2024 Aug 1. PMID: 39087762.

    - Designing microfluidic (microscopic volumes of liquid) assays for probing neutrophil-borrelia interactions in blood during acute Lyme disease. (NIAID; R21AI156723)
    - Evaluating a hybrid enzyme-linked immunosorbent assay (detects the presence of a specific molecule) for Lyme disease detection. (NIAID; R44AI142903)
    - Optimizing platform development for both diagnostics and vaccine development for TBDs. (NIAID: U19AI181960 and U19AI181930)
- Investigated vaccine and adjuvant (substance that increases the immune response to a vaccine) development against Lyme disease by:
    - Developing a vaccine against *Borrelia* species by combining peptides based on outer-membrane proteins expressed in various phases of *B. burgdorferi* infectious cycle with novel adjuvants. (NIAID; R01AI152219)
    - Developing an intranasal vaccine against Lyme disease. (NIAID; R44AI167605)
    - Developing a novel subunit Lyme disease vaccine with a combination adjuvant composed of two Toll-like receptor (early immune system response protein) agonists. (NIAID)
- Identified two compounds that bind to a key component of the bacterial nutrient transport system (OppA2) and significantly slow bacterial growth.[1445,1446] (NIAID)
- Demonstrated that the antibiotic hygromycin A selectively kills the Lyme-causing bacterium *B. burgdorferi* without harming beneficial gut bacteria in mouse models.[1447] (NIAID)
- Worked toward commercializing a DNA-sequencing technology as a sensitive molecular diagnostic assay for detection of Crimean-Congo hemorrhagic fever virus. (NIAID; R44AI157650)
- Demonstrated that a vaccine against Crimean Congo hemorrhagic fever was effective in pre-clinical models.[1448,1449] (NIAID)
- Worked toward isolating broadly protective monoclonal antibodies for Crimean-Congo hemorrhagic fever virus. (NIAID; R01AI180125)
- Assessed adjuvants against severe fever with thrombocytopenia syndrome virus. (NIAID)

Clinical Research

- Established a population of patients with Lyme disease for evaluation, treatment, and follow-up to learn more about the infection. (NIAID; NCT00028080)
- Assessed the human immune response to the *Ixodes scapularis* tick bite. (NIAID; NCT05036707)
- Demonstrated that most pediatric patients treated for all stages of Lyme disease reported full resolution of symptoms within six months.[1450] (NIAID)
- Investigating the role of IgE antibodies in AGS, alpha-gal red meat allergy, and in development of human disease in response to the tick bite.[1451] (NIAID)

Malaria

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. In 2023,

[1445] https://www.niaid.nih.gov/news-events/lyme-transport
[1446] Holly KJ, et al. Front Antibiot. 2024 May 20;3:1395425. PMID: 39816271.
[1447] Leimer N, et al. Cell. 2021 Oct 14;184(21):5405-5418.e16. Epub 2021 Oct 6. PMID: 34619078.
[1448] Hawman DW, et al. NPJ Vaccines. 2024 May 20;9(1):86. PMID: 38769294.
[1449] https://www.niaid.nih.gov/news-events/cchf-model
[1450] Monaghan M, et al. Pediatr Res. 2024 Jan;95(1):174-181. Epub 2023 Mar 30. PMID: 36997691.
[1451] R37AI020565, R01AI172112, R01AI182247, and R01AI135049

there were an estimated 263 million malaria cases and 597,000 malaria deaths worldwide.[1452] However, Malaria is not endemic in the U.S. and does not regularly occur or spread. In a typical year, the U.S. reports about 2,000 cases of malaria, most of which are in people who contract malaria while traveling to another country.[1453] Malaria is characterized by fever and flu-like symptoms and can be deadly if not diagnosed and treated quickly. Pregnant women are particularly vulnerable to malaria infections, as infections during pregnancy put the fetus at increased risk of experiencing adverse outcomes. Considerable progress has been made in the global fight to control and eliminate malaria through improved prevention and control efforts. NIH is leveraging its comprehensive research program to achieve the goal of eliminating malaria. Below are select malaria research advances and highlights for FY22 to FY24.

Epidemiological Research

- Evaluated the flow of malaria parasites and drug resistance within the Democratic Republic of Congo and across its borders. (NIAID; R01AI139520)
- Aimed to better understand the impacts of environment, host genetics, and antigen variability on malaria vaccine efficacy. (NIAID; R01AI137410)
- Took steps to improve the accuracy of malaria surveillance with serology and parasite genetic data. (NIAID; K23AI166009)
- Evaluated a resurgence of malaria after seven years of intensive vector control interventions in Eastern Uganda.[1454] (NIAID; U19AI089674)
- Examined urban malaria, the role of *Anopheles stephensi*, urbanization, and other determinants in Eastern Ethiopia.[1455] (NIAID; U19AI129326)

Fundamental Research

- Uncovered evidence that malaria infection of the placenta may reduce the amount of glucose that passes to the fetus.[1456] (NICHD, NIAID)
- Explored mosquito immune responses and malaria transmission. (NIAID; ZIAAI000947)
- Examined epitopes on malaria antigens. (NIAID; R01AI153425)
- Evaluated the immune response to malaria infection by:
    - Studying mechanisms underlying the disruption of the blood-brain barrier during cerebral malaria. (NIAID; R01AI181219)
    - Understanding the differentiation, function, and maintenance of parasite-specific memory CD4 T cells that play an important role in the adaptive immune system and are critical for resistance to blood stage *Plasmodium* infection. (NIAID; R01AI125446)
    - Investigating antibody responses to early childhood malaria infections to inform vaccine development. (NIAID; R21AI176009)
    - Identifying mechanisms that trigger immune dysregulation during malaria infection. (NIAID; R01AI167058)

[1452] https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024
[1453] https://www.cdc.gov/malaria/index.html
[1454] Kamya MR, et al. PLOS Glob Public Health. 2024 Aug 29;4(8):e0003254. PMID: 39208072.
[1455] Merga H, et al. Malar J. 2024 Oct 9;23(1):303. PMID: 39385192.
[1456] Mosavati B, et al. Sci Rep. 2022 Sep 10;12(1):15278. PMID: 36088464.

- Demonstrated that malaria parasites resistant to the drug atovaquone struggle to survive and develop in mosquitoes, potentially reducing spread in the field.[1457] (NIAID)
- Discovered that malaria parasites sense environmental changes and subsequently switch antigens to evade the human immune system.[1458] (NIAID)

Translational Research

- Evaluated an antimalarial compound that cured *P. falciparum* malaria infection in a mouse model. (NCATS; ZIATR000013)
- Developed insights into the role of dysregulated inflammation during blood-stage *Plasmodium* infection and identifying pathways that could be exploited to enhance immunity to *Plasmodium*.[1459] (NCATS; UL1TR000114)
- Demonstrated that cipargamin, a novel antimalarial drug, achieved rapid clearance of the *P. falciparum* malaria parasite.[1460] (FIC)
- Launched a study to determine whether Neuregulin-1, a small protein, can reduce brain damage and mortality in a mouse model of human cerebral malaria. (NINDS; R01NS125775)
- Investigated malaria vaccine research and development by:
    - Engineering malaria vaccines that target the asymptomatic liver stage (which proceeds the symptomatic red blood stage) of the malaria lifecycle by targeting vulnerable epitopes in the parasite-secreted circumsporozoite protein. (NIAID; R01AI169739)
    - Expanding the breadth, magnitude, and durability of PfSPZ vaccines (active non-replicating whole sporozoites, the parasite stage injected into the blood by a mosquito bite) by creating multi-strain vaccines, designer hybrid and genetically altered parasite vaccines, and use of unique adjuvant. (NIAID; U01AI155356)
    - Demonstrating safety and protective efficacy of PfSPZ-LARC2, a next-generation vaccine strain that uses a different method of attenuating whole sporozoites.[1461] (NIAID)
    - Accelerating malaria vaccines with a custom preclinical mouse model platform that more accurately replicates human biology (NIAID; R01AI168114)
- Invested in the optimization of assays to aid in developing malaria vaccines. (NIAID; ZIAAI001056 and ZIAAI001008)
- Focused on developing a malaria vaccine for pregnant women. (NIAID; ZIAAI001176)
- Demonstrated that a new antimalarial drug, MED6-189, slows the growth of and kills both drug-sensitive and drug-resistant malaria-causing parasite strains.[1462] (NIAID)
- Assessed malaria vaccine immunity and correlates of protection by:
    - Investigating baseline host and environmental factors that impact pre-red blood cell malaria vaccine responsiveness in endemic regions. (NIAID; U01AI165745)
    - Integrating human and non-human primate data to understand the acquisition of pre-red blood cell immunity in the face of previous malaria exposure. (NIAID; U01AI165457)

[1457] Balta VA, et al. Nat Commun. 2023 Oct 12;14(1):6415. PMID: 37828012.

[1458] Schneider VM, et al. Proc Natl Acad Sci U S A. 2023 Apr 25;120(17):e2302152120. Epub 2023 Apr 17. PMID: 37068249.

[1459] Bravo M, et al. J Immunol. 2024 Mar 15;212(6):992-1001. PMID: 38305633.

[1460] Schmitt EK, et al. Clin Infect Dis. 2022 May 30;74(10):1831-1839. PMID: 34410358.

[1461] Goswami D, et al. EMBO Mol Med. 2024 Apr;16(4):723-754. Epub 2024 Mar 21. PMID: 38514791.

[1462] Chahine Z, et al. Science. 2024 Sep 27;385(6716):eadm7966. Epub 2024 Sep 27. PMID: 39325875.

- Evaluating malaria vaccine performance in endemic regions of Kenya using a systems immunology approach. (NIAID; U01AI165524)
- Showing that maternal antibodies interfere with the effectiveness of a malaria vaccine in infants, leading to lower immune responses.[1463] (NIAID)

Clinical Research

- Completed Phase 1 clinical trials of a malaria vaccine in Malian adults. (NIAID; NCT05135273)
- Demonstrated that PfSPZ vaccine was safe and well tolerated in adults in Mali and showed significant efficacy against high levels of *P. falciparum* in the blood and clinical malaria.[1464] (NIAID)
- Showed that one dose of a monoclonal antibody was safe and highly protective from malaria infection in healthy, non-pregnant adults.[1465] (NIAID)
- Illustrated that subcutaneous administration of the L9LS monoclonal antibody to children was protective against *P. falciparum* infection and clinical malaria over a six-month period.[1466] (NIAID)
- Established that pregnant women in Mali develop antibodies over multiple pregnancies that help protect against malaria-related complications in their infants.[1467] (NIAID)
- Determined that risk of *P. vivax* recurrence is substantially lower for higher dose primaquine treatment in Cambodia.[1468] (NIAID)
- Initiated a Phase 1/2 trial testing a novel drug in pediatric cerebral malaria. (NIAID; NCT05478720)
- Demonstrated that low-dose intravenous and subcutaneous administration of two different monoclonal antibodies each conferred protection against malaria in U.S. adults.[1469,1470] (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.[1471] WNV is well established in the U.S. (average of around 2,000 reported cases per year since 2010)[1472] and many countries in Europe and the Middle East. Symptoms include fever, headache, weakness, gastrointestinal symptoms, and rash. In less than one percent of cases, WNV can cause neuroinvasive disease such as encephalitis, meningitis, or acute flaccid myelitis.[1473] 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. Below are select WNV research advances and highlights for FY22 to FY24.

Epidemiological Research

[1463] Macià D, et al. Lancet Infect Dis. 2025 Mar;25(3):335-345. Epub 2024 Oct 23. Erratum in: Lancet Infect Dis. 2025 Mar;25(3):e137. PMID: 39461358.
[1464] Diawara H, et al. Lancet Infect Dis. 2024 Dec;24(12):1366-1382. Epub 2024 Aug 14. PMID: 39153490.
[1465] Kayentao K, et al. N Engl J Med. 2022 Nov 17;387(20):1833-1842. Epub 2022 Oct 31. PMID: 36317783.
[1466] Kayentao K, et al. N Engl J Med. 2024 May 2;390(17):1549-1559. Epub 2024 Apr 26. PMID: 38669354.
[1467] Mahamar A, et al. Front Immunol. 2024 Jan 11;14:1330962. PMID: 38274790.
[1468] Eng V, et al. Lancet Infect Dis. 2025 Mar 17:S1473-3099(25)00033-7. Epub ahead of print. PMID: 40112852.
[1469] Lyke KE, et al. Lancet Infect Dis. 2023 May;23(5):578-588. Epub 2023 Jan 25. PMID: 36708738.
[1470] Wu RL, et al. N Engl J Med. 2022 Aug 4;387(5):397-407. PMID: 35921449.
[1471] https://www.cdc.gov/west-nile-virus/php/transmission/index.html
[1472] https://www.cdc.gov/west-nile-virus/data-maps/historic-data.html
[1473] https://www.cdc.gov/west-nile-virus/hcp/clinical-signs/

- Observed that approximately 35 percent of patients hospitalized for severe WNV disease have auto-antibodies that neutralize two types of interferons (signaling proteins produced in response to viral infection), and that the prevalence is highest in patients with encephalitis.[1474] (NIDDK and NIAID)
- Evaluated encephalitis in horses and revealed unnoticed circulation of WNV in Brazil.[1475] (NIAID)

Fundamental Research

- Aimed to identify the initial cells infected by WNV and how this may contribute to pathogenesis and infection of the brain. (NIAID; R01AI166594)
- Assessed the role of WNV-host protein interactions in evading immunity. (NIAID; R01AI143850)
- Evaluated the innate immune mechanisms controlling flavivirus capacity to damage the nervous system, including the brain. (NIAID; R01AI183793)
- Studied meningeal immunity and viral neuropathogenesis (development of disease in the brain) of flaviviruses. (NIAID; R01AI183879)
- Established that mice which lack certain immune responses are effective for studying how WNV interacts with mosquitoes.[1476] (NIAID)
- Developed a new method that combines two genetic sequencing techniques to quickly and accurately detect and differentiate between multiple viruses like CHIKV, DENV, ZIKV, yellow fever, and WNV in a single test.[1477] (NIAID)

Translational Research

- Aimed to develop a Toll-like receptor 4 agonist (molecule that activates the receptor) as a vaccine adjuvant for inclusion in vaccines to better protect against WNV infection. (NIAID)
- Assessed diagnostic, adjuvant, and vaccine development in the context of vaccines for ZIKV, ENV, and WNV. (NIAID; U19AI181960)
- Evaluated a candidate subunit vaccine for Powassan Virus and WNV adjuvanted with Alhydroxiquim-II, a small molecule attached in a unique way to Alhydrogel, a substance frequently called alum that is the most commonly used adjuvant in vaccines for people. (NIAID)

Zika

Zika virus (ZIKV) is primarily transmitted to humans through the bite of infected *A. aegypti* mosquitoes.[1478] Its name comes from the Zika Forest of Uganda, where the virus was first isolated in 1947; however, it is relatively new to the Americas. 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. There have been no reports of Zika virus transmission by mosquitoes in the continental U.S. since 2018.[1479]

In adults, ZIKV infection causes mild symptoms like fever, rash, headache, and joint and muscle pain. In more rare cases, it has been linked to various neurological complications, such as Guillain-Barré syndrome,

[1474] Gervais A, et al. J Exp Med. 2023 Sep 4;220(9):e20230661. Epub 2023 Jun 22. PMID: 37347462.
[1475] Fritsch H, et al. Viruses. 2022 Jul 14;14(7):1540. PMID: 35891521.
[1476] Baldon L, et al. Trop Med Infect Dis. 2024 Sep 2;9(9):201. PMID: 39330890.
[1477] Xavier J, et al. Viruses. 2023 Dec 22;16(1):23. PMID: 38257724.
[1478] https://www.cdc.gov/zika/about/index.html
[1479] https://www.cdc.gov/zika/zika-cases-us/index.html

transverse myelitis, and ophthalmological manifestations that persist after the acute phase of the infection. In addition to being transmitted by mosquito bite, ZIKV can be sexually transmitted from a person who is infected, even if asymptomatic, to their sex partners.[1480] More concerningly, ZIKV can be transmitted from an infected woman to her baby during pregnancy and can result in serious birth defects, including microcephaly. Even when initially asymptomatic, many children borne to ZIKV-infected mothers later develop motor, cognitive, and sensory problems.[1481] 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. Below are select Zika research advances and highlights for FY22 to FY24.

Epidemiological Research

- Aimed to understand the interaction between pathogenesis and blood transfusion during acute viral infections. (NHLBI; R01HL153073)
- Assessed the impact of severe congenital Zika virus syndrome (CZS) on the medical and developmental outcomes for children. (NICHD; R01HD112407)
- Identified school age abnormalities in neurodevelopment and evaluated brain structural and functional differences among children with ZIKV exposure *in utero* who do not have CZS. (NICHD; R01HD102445 and NCT04398901)

Fundamental Research

- Assessed the role of viral genetics and the factors that cause CZS in some but not all infected mothers. (NHLBI; R01HL105704)
- Studied molecular regulatory mechanisms of Zika virus-induced intracranial calcifications (abnormal accumulation of calcium in the brain). (NIDCR)
- Expanded a study to define the craniofacial and dental phenotypes of children exposed to the ZIKV during gestation. (NIDCR)
- Launched a study to investigate the impact of postnatal ZIKV infection on brain development and behavior using a rhesus macaque model. (NINDS; R01NS120182)
- Investigated the role of the JAK-STAT protein signaling pathway in Zika Virus-induced fetal injury. (NIAID; R01AI143265)
- Studied the mechanisms of viral pathogenesis in the central nervous system. (NIAID)
- Assessed Zika risk during pregnancy by:
    - Assessing previous exposure to Dengue as a risk factor for Zika. (NIAID; R01AI132563)
    - Investigating how antibodies against DENV enhance infection and pathogenesis of ZIKV in the context of pregnancy. (NIAID; R01AI150837)
    - Finding ZIKV variability is maintained during early transmission from placenta to fetus but reduced in fetal bodies and brains at late stages of infection.[1482] (NIAID)
- Explored host immune responses to ZIKV infection by:
    - Determining how immune-regulatory proteins cooperate to regulate complex anti-viral defense programs and understand how those responses protect against Dengue and ZIKV infections. (NIAID; K08AI130381)

[1480] https://www.cdc.gov/zika/hcp/sexual-transmission/index.html
[1481] https://www.cdc.gov/zika/signs-symptoms/index.html
[1482] Evans AB, et al. PLoS Negl Trop Dis. 2023 Oct 5;17(10):e0011657. PMID: 37796973.

    - Studying innate immune regulation (body's first line of defense against pathogens through various physical and chemical barriers) of ZIKV infection. (NIAID; R01AI145296)
    - Assessing innate immunity of ZIKV infection in human neural progenitors (precursor cells that give rise to neurons). (NIAID; K08AI150996)
    - Evaluating the role of the enzyme ADAR1 in suppressing ZIKV replication and infection in retinal cells of the eye. (NIAID; R21AI149385)
- Demonstrated ZIKV modulates host cellular metabolism to increase viral replication.[1483] (NIAID)
- Determined that ZIKV can infect human placentas in the absence of maternal factors.[1484] (NIAID)
- Found that ZIKV exposure during pregnancy in non-human primates can severely disrupt the development of myelin in the fetal brain, which is crucial for brain function.[1485] (NIAID)
- Showed that prior infection with ZIKV can increase risk of symptomatic DENV infection.[1486] (NIAID)

Translational Research

- Utilized high-throughput systems biology approaches to identify critical host cell pathways for ZIKV replication.[1487] (NCATS)
- Advanced novel vaccines and adjuvants by:
    - Demonstrating that a ZIKV T-cell based DNA vaccine promotes protection from ZIKV infection in the absence of neutralizing antibodies.[1488] (NIAID)
    - Testing a novel, live-attenuated Zika vaccine with the starting region of mRNA, called the 5' untranslated region, modified. (NIAID; R15AI178654)
    - Evaluating a novel vaccine against ZIKV based on the mosquito salivary gland protein AgBR1. (NIAID; R42AI142846)
- Assessed DENV-ZIKV correlates of cross-protection in non-human primates. (NIAID; R01AI148264)
- Identified a role for IgM antibodies (one of five antibody classes and serves as the first line of defense against infections) in protection against ZIKV.[1489] (NIAID)

Clinical Research

- Assessed alterations in acyl-carnitine (important for transporting fat molecules) and fatty acid metabolism in red blood cells from ZIKV positive donors. (NHLBI; R21HL150032)
- Demonstrated that children with microcephaly due to CZS are noticeably delayed in their neural development, including communication skills.[1490] (NIDCD)
- Evaluated antibody responses elicited by Zika vaccination in individuals with no prior flavivirus exposure and in individuals previously infected with flavivirus. (NIAID; R01AI155983)

Other Vector-Borne Diseases

[1483] Branche E, et al. Nat Commun. 2022 Sep 12;13(1):5341. PMID: 36097162.
[1484] Villazana-Kretzer DL, et al. Commun Biol. 2022 Mar 18;5(1):243. PMID: 35304593.
[1485] Tisoncik-Go J, et al. Nat Commun. 2024 Jun 18;15(1):5173. PMID: 38890352.
[1486] Zambrana JV, et al. Sci Transl Med. 2024 May 29;16(749):eadn2199. Epub 2024 May 29. PMID: 38809964.
[1487] Song G, et al. Genomics Proteomics Bioinformatics. 2021 Feb;19(1):108-122. Epub 2021 Feb 19. Erratum in: Genomics Proteomics Bioinformatics. 2022 Aug;20(4):808-809. PMID: 33610792.
[1488] Roth C, et al. PLoS Negl Trop Dis. 2024 Oct 17;18(10):e0012601. PMID: 39418312.
[1489] Singh T, et al. Cell. 2022 Dec 8;185(25):4826-4840.e17. Epub 2022 Nov 18. PMID: 36402135.
[1490] Key AP, et al. Ear Hear. 2024 Jul-Aug 01;45(4):850-859. Epub 2024 Feb 5. PMID: 38363825.

NIH supports research on many other VBDs in addition to those covered above. These include, but are not limited to, Rift Valley fever,[1491] Yellow fever,[1492] Chagas disease,[1493] Leishmaniasis,[1494] and equine encephalitis.[1495] These diseases pose significant public health challenges in various regions of the world—including the U.S., although in more limited capacity—often leading to severe illness and economic burden. Below are select research advances and highlights for the FY22 to FY24 reporting period.

Epidemiological Research

- Identified a highly sensitive immunological marker against two mosquito salivary proteins.[1496,1497] (NIAID)
- Investigated co-circulation of VBDs in a region hyperendemic for malaria (prevalence around 45 percent) and found the presence of infection (current or past) for DENV was 77 percent, ZIKV was 31 percent, and CHIKV was 26 percent.[1498,1499] (NIAID)
- Evaluated the combined set of all genes thought to be involved in mosquito-borne diseases and compared geographical patterns, range expansion, and future disease emergence.[1500,1501,1502,1503] (NIAID)
- Isolated a newly recognized virus from sandflies in China, named Hedi virus, that is a member of the phlebovirus genus.[1504] (NIAID)
- Recognized a potential role of pre-existing, heterologous immunity from other flavivirus (DENV or ZIKV) in preventing transmission of yellow fever virus.[1505] (NIAID)

Fundamental Research

- Assessed improved serological diagnostic and parasite genotyping tools for *Trypanosoma cruzi*, the parasitic protozoa that causes Chagas disease. (NICHD; R01HD094955)
- Described a novel mechanism that host natural antibodies can help Leishmania parasites clump together, promoting genetic exchange, and enhancing their survival and adaptability.[1506] (NIAID)
- Established a mechanism of flavivirus cross protection against Yellow Fever.[1507] (NIAID)

Translational Research

[1491] https://www.cdc.gov/rift-valley-fever/about/index.html
[1492] https://www.cdc.gov/yellow-fever/index.html
[1493] https://www.cdc.gov/chagas/index.html
[1494] https://www.cdc.gov/leishmaniasis/about/index.html
[1495] https://www.cdc.gov/eastern-equine-encephalitis/about/index.html
[1496] Chea S, et al. Front Immunol. 2024 May 1;15:1368066. PMID: 38751433.
[1497] https://www.niaid.nih.gov/news-events/new-tool-identifies-aedes-mosquito-exposure-people
[1498]Bane S, et al. Am J Trop Med Hyg. 2024 Jun 4;111(1):107-112. PMID: 38834052.
[1499] https://www.niaid.nih.gov/news-events/arbovirus-blog
[1500] Bernardi V, et al. Emerg Infect Dis. 2025 Apr;31(4):851-854. PMID: 40133058.
[1501] Situma S, et al. BMJ Glob Health. 2024 Jun 10;9(6):e014737. PMID: 38857944.
[1502] Yaro AS, et al. Front Epidemiol. 2022 Oct 13;2:1001782. PMID: 38455321.
[1503] Lehmann T, et al. Proc Biol Sci. 2023 Nov 29;290(2011):20231581. Epub 2023 Nov 29. PMID: 38018102.
[1504] Xu Z, et al. Viruses. 2021 Apr 27;13(5):772. PMID: 33925561.
[1505] Shinde DP, et al. Nat Commun. 2024 Nov 10;15(1):9728. PMID: 39523371.
[1506] Serafim TD, et al. Nature. 2023 Nov;623(7985):149-156. Epub 2023 Oct 25. PMID: 37880367.
[1507] Shinde DP, et al. Viruses. 2024 May 24;16(6):836. PMID: 38932129.

- Identified a set of compounds that inhibit La Crosse virus-induced cell death in neuronal cell lines.[1508] (NCATS)
- Advanced development of monoclonal antibodies for Yellow Fever virus.[1509,1510] (NIAID)
- Progressed maturation of multiplex point-of-care diagnostics for arboviruses by:
    - Creating a serology assay using part of an envelope protein that distinguishes between Zika virus and DENV and can accurately identify the history of previous infection with either Zika or DENV.[1511] (NIAID)
    - Developing serodiagnostic and point-of-care detection assays for arboviruses, including mosquito-borne viruses. (NIAID; R01AI155735 and R01AI149502)
    - Exploring rapid, DNA-sequencing free diagnostics of arboviral diseases in resource limited settings. (NIAID; R01AI155959)
- Advanced vaccine and therapeutic antibody development for arboviruses.[1512] (NIAID)
- Provided information defining the humoral (antibody) immune response and correlates of protection for alphavirus infections. (NIAID; R01AI172156)

Clinical Research

- Demonstrated that a vaccine for eastern equine encephalitis virus, western equine encephalitis virus, and Venezuelan equine encephalitis virus was safe, well-tolerated, and induced a neutralizing antibody response in adult volunteers.[1513] (NIAID)
- Completed a Phase 3 study quantifying the epidemiological impact of targeted indoor residual spraying on *Aedes* mosquito-borne diseases. (NIAID; NCT04343521)
- Evaluated the safety, reactogenicity (capacity to produce an expected immune reaction), and immunogenicity of the vaccine candidate ShistoShield against schistosomiasis in a Phase 1 study. (NIAID; NCT05292391)

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. Below are select vector control research advances and highlights for FY22 to FY24.

Fundamental Research

[1508] Ojha D, et al. Nat Microbiol. 2021 Nov;6(11):1398-1409. Epub 2021 Oct 21. PMID: 34675384.
[1509] Ricciardi MJ, et al. Sci Transl Med. 2023 Mar 29;15(689):eade5795. Epub 2023 Mar 29. PMID: 36989376.
[1510] Crunkhorn S, et al. Nat Rev Drug Discov. 2023 May;22(5):355. PMID: 37020013.
[1511] Hein LD, et al. Lancet Microbe. 2025 Feb;6(2):100951. Epub 2024 Dec 25. PMID: 39730005.
[1512] U19AI181881, U19AI181984, U19AI181968, U19AI181960
[1513] Coates EE, et al. Lancet Infect Dis. 2022 Aug;22(8):1210-1220. Epub 2022 May 11. PMID: 35568049.

- Developed a framework to remove genetically inserted gene sequences from modified mosquito strains, an important step for advancing genetics-based mosquito control.[1514] (NIAID)
- Advanced a method for cryopreservation of mosquito vectors of human pathogens.[1515] (NIAID)

Translational Research

- Demonstrated that genetically engineered mosquitoes produce a human protein that blocks a key enzyme used by malaria-causing parasites, significantly reducing the transmission of malaria to both rodents and humans from mosquitoes.[1516] (NIAID)

Clinical Research

- Evaluated the efficacy of wolbachia-infected *Aedes aegypti* mosquitoes in reducing the incidence of arboviral infection in Brazil (wolbachia is a common bacterium that infects mosquitos and it has been linked to viral resistance in mosquitos). (NIAID; R01AI182096 and NCT04514107)
- Assessed repeat ivermectin mass drug administration for malaria control. (NIAID; NCT03967054)

Committees, Programs, and Workshops

Committees

- Trans-NIH Tick-Borne Diseases Strategic Planning Team was convened with subject matter 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 VBDs, particularly vector control. (NIAID)
- The HHS Tick-borne 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. (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 (Biomedical Advanced Research and Development Authority, CDC, DoD, FDA, NIH, Walter Reed Army Institute of Research) 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)

[1514] Chae K, et al. PNAS Nexus. 2022 Mar 30;1(2):pgac037. PMID: 36713320.
[1515] Gallichotte EN, et al. Cryobiology. 2021 Apr;99:1-10. Epub 2021 Feb 5. PMID: 33556359.
[1516] Pascini TV, et al. Nat Commun. 2022 May 26;13(1):2949. PMID: 35618711.

- Vector-Borne Disease National Strategy Federal Working Group. Comprised of over 50 participants from multiple NIH institutes, including NIAID, as well as more than 15 federal agencies, this effort aims to produce a VBD national strategy. This strategy will: identify gaps and unnecessary duplication in federally funded programs, define strategic goals to address VBDs, and set benchmarks to measure progress toward achieving such goals. (NIAID)

Programs

- 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 is a transfusion safety research program designed to evaluate and improve the safety and availability of the blood supply and of transfused products. The current program is poised to conduct and evaluate an emerging infectious agent quickly for its incidence and prevalence among blood donors, transfusion-transmission potential, risk factors, and clinical relevance to the blood recipient population. It has conducted research to detect and report changes in the incidence of arboviruses of paramount public health importance such as ZIKV, DENV, and CHIKV. Data and results from this body of research continue to inform and impact the U.S. and global blood screening policies and strategies for preventing transmission of these viruses via blood transfusion, and implementation of enhanced blood safety measures. (NHLBI)
- Therapeutics for Rare and Neglected Diseases program encourages and speeds the development of new treatments for diseases with high unmet medical needs. This includes tropical VBDs, such as schistosomiasis and malaria. The program 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 VBDs. 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)
- Immune Response to Arthropod Blood Feeding program was designed to understand the immunologic events that occur during blood feeding by hematophagous arthropods (those that feed on blood), which facilitate vector-borne pathogen transmission. NIH has received grant applications focused on vector-borne pathogens including arboviruses (e.g., DENV, ZIKV, Powassan virus, and Crimean-Congo hemorrhagic fever virus), *B. burgdorferi*, *Plasmodium vivax*, Leishmania, *Orientia tsutsugamushi*, *Trypanosoma brucei*, and *Ehrlichia chaffeensis*. (NIAID)
- Collaborative Cross Mouse Model Generation and Discovery of Immunoregulatory Mechanisms program was designed to support the use of Collaborative Cross mouse lines to advance understanding of the host genetics involved in immune regulation and function and to further develop Collaborative Cross mouse lines that more faithfully reproduce human immune responses. NIH has received grant applications focused on vector-borne pathogens including *B. burgdorferi*, *Plasmodium yoelii*, *Borrelia recurrentis*, West Nile Virus, Japanese Encephalitis Virus, Powassan Virus, and Rift Valley fever virus. (NIAID)

- The Centers for Research in Emerging Infectious Diseases 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 conduct pathogen/host surveillance; study pathogen transmission, pathogenesis and immunologic responses in the host; and develop reagents and diagnostic assays for improved detection for important emerging pathogens and their vectors. They developed a framework and the infrastructure necessary to respond quickly and effectively to future outbreaks. (NIAID)
- National Public Health Strategy to Prevent and Control Vector-Borne Diseases in People represents the largest formal federal coordination effort focused on VBD prevention and control with contributions by over 50 representatives across 17 federal agencies. (U.S. Government-wide)
- The Models of Infectious Disease Agent Study is a network of researchers who develop and use computational, statistical, and mathematical models to improve the understanding of emerging infectious disease dynamics. The Coordination Center[1517] plays a key role in developing collaborative activities and hosting educational opportunities to enhance the utility of shared infectious disease modeling resources, advance disease modeling science, and improving training opportunities, while coordinating communication among network members, including graduate students and postdoctoral researchers, and public health practitioners. Vector-borne disease modeling is included among the infectious disease research topics investigated by the network members. (NIGMS)
- NIEHS Worker Training Program (Ebola, Covid-19 and H1N1) awards recipients delivering stand-alone infectious disease and biological hazards training courses or integrating content into their hazardous materials and hazardous waste curricula. The programs offer a wide variety of courses to support this effort. Recent training tools in infectious disease can be found on the Worker Training Program Infectious Disease page.[1518] (NIEHS)
- The NIAID Vaccine Adjuvant Discovery Program supports the systematic screening for novel immunostimulators and immunomodulators that can be used for preventive vaccines against a wide variety of pathogens. The program directly supported the discovery of novel agonists for DENV and CHIKV vaccines and adjuvant selection for a severe fever with thrombocytopenia syndrome virus vaccine. Researchers can access information about NIAID-supported adjuvants through the Vaccine Adjuvant Compendium, which expanded in FY22 to FY24 to include a greater number of adjuvants.[1519] (NIAID)
- NIAID's Immune Epitope Discovery program is comprised of two complementary initiatives: 1) Innovations in Functional B Cell Epitope Discovery, and 2) T Cell Immune Epitope Discovery and Mechanisms of T Cell Protection. Together, these programs support the discovery and functional characterization of novel epitopes associated with human responses to pathogens that cause chronic or acute infection or are associated with human allergic responses, development of autoimmune disease, or tissue/organ transplant rejection. The Immune Epitope Database and Tools curates and makes publicly available immune epitopes from the NIAID discovery program and elsewhere in the scientific literature.[1520] (NIAID)

[1517] https://midasnetwork.us/
[1518] https://tools.niehs.nih.gov/wetp/index.cfm?id=2554
[1519] https://vac.niaid.nih.gov/
[1520] https://www.iedb.org/

- The Research and Development of Vaccines and Monoclonal Antibodies for Pandemic Preparedness Network is a collaborative research network conducting basic and translational research to develop generalizable vaccines and monoclonal antibody strategies using representative viruses within virus families. The Network launched in Fall of 2024 with seven Research Centers located across the U.S. and one Coordination and Data Sharing Center. The Research Centers study vector-borne viruses that cause disease in the U.S., including Dengue, Chikungunya, West Nile, Venezuelan Equine Encephalitis, Western Equine Encephalitis, La Crosse Encephalitis, and Cache Valley viruses, among others. (NIAID)

Workshops

- *Incorporating Systems Biology to Vector-Borne Pathogen Research: Current Landscape, Challenges, and Opportunities* (2022) brought together experts in arthropod vectors/vector-borne diseases and computation/modeling to explore systems biology approaches in both the vertebrate and invertebrate host to spark ideas about accelerating research. (NIAID)
- The Workshop on *Pandemic Preparedness: The Prototype Pathogen Approach to Accelerate Medical Countermeasures – Vaccines and Monoclonal Antibodies* (2022) had several goals, including describing the prototype pathogen approach, selecting prototype pathogens for future study, and identifying knowledge gaps within the selected viral families. Prototype viruses being considered for study within the 10 families of pandemic concern included several VBDs. (NIAID)
- *Continuing Development of Vaccines and Monoclonal Antibodies against Zika Virus* (2023) assembled experts in epidemiology, immunology, virology, healthcare, industry, non-profit administration, and government with the goals of updating countermeasure developers on the latest scientific information, encouraging new collaborations between academic researchers and industry, and providing a regulatory perspective on the development of countermeasures for ZIKV.[1521] (NIAID)

[1521] Woodson SE, et al. NPJ Vaccines. 2024 May 24;9(1):91. PMID: 38789469.

Appendix D: NIH Institute and Center Research Collaborations

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.[1522] 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. NIH-wide 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 ICs 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 health of all Americans.

For full information about FY22 to FY24 NIH IC research collaborations, see the *NIH Collaborations Report*: https://dpcpsi.nih.gov/sites/g/files/mnhszr346/files/2026-02/NIH%20IC%20Research%20Collaboration%20Report%20FY%202022-24_Cleaned%20for%20Publication_4.pdf

For previous reports, see: https://dpcpsi.nih.gov/collaboration/reports

[1522] https://www.nih.gov/institutes-nih

Appendix E: Research Training and Graduate Medical Education Data

Table 6. National Research Service Award (NRSA) Research Training Programs: Number of Ph.D. Recipients by Field of Study[1523]

Field of Study: Broad and Major Category	Field of Study: Description	PhD FY: 2021	PhD FY: 2022	PhD FY: 2023
Agricultural sciences and natural resources	**Overall**	**21**	**14**	**19**
Agricultural sciences	Subtotal	21	12	15
Agricultural sciences	Agricultural and horticultural plant breeding	0	0	1
Agricultural sciences	Agricultural sciences/natural resources, other	1	0	0
Agricultural sciences	Animal nutrition	0	0	0
Agricultural sciences	Animal science, poultry or avian	0	0	0
Agricultural sciences	Animal sciences, other	2	2	4
Agricultural sciences	Food science	4	0	1
Agricultural sciences	Food science and technology, other	0	0	0
Agricultural sciences	Horticulture science	0	1	1
Agricultural sciences	Plant pathology/phytopathology (agricultural sciences)	2	0	1
Agricultural sciences	Plant sciences, other	1	0	0
Agricultural sciences	Soil chemistry/microbiology	0	1	0
Agricultural sciences	Veterinary sciences	11	8	7
Natural resources and conservation	Subtotal	0	2	4
Natural resources and conservation	Environmental science	0	2	3
Natural resources and conservation	Natural resources and conservation	0	0	1
Natural resources and conservation	Natural resources/environmental economics (agricultural sciences)	0	0	0
Biological and biomedical sciences	**Overall**	**2,346**	**2,677**	**2,747**
Biochemistry and biophysics	Subtotal	210	245	257

[1523]Data drawn from IMPAC II Current Files and Doctorate Records File (DRF) as of 6/5/2025 and are subject to change. Table 7 has adopted the SED-CIP taxonomy for broad and major field classification from the NSF DRF. According to the National Center for Science and Engineering Statistics, beginning in 2021 a (https://ncses.nsf.gov/pubs/ncses23200) modified version of the 2020 Classification of Instructional Programs (CIP) codes was used for data collection, and the new broad, major, and detailed fields were applied in tables reporting only the most recent data year. Therefore, field of doctorate data in 2021 may not be directly comparable to prior years. To maintain consistency with past data, we kept the same field of study codes for detailed fields, while adopting the CIP-based categorization for broad and major fields. This updated approach provides a more detailed, yet still broad aggregation of fields compared to historical classifications used in earlier SED data tables. For example, the "Agricultural sciences and natural resources" and "Biological and biomedical sciences" broad categories were formerly minor categories included within the "Life Sciences" broad category. The following fine fields were removed in this version: Fishing and fisheries sciences/management, Paleontology, Industrial and organizational psychology, and Engineering management and administration. CTSA trainees are included in the NRSA data provided.

Field of Study: Broad and Major Category	Field of Study: Description	PhD FY: 2021	PhD FY: 2022	PhD FY: 2023
Biochemistry and biophysics	Biochemistry (biological sciences)	157	206	200
Biochemistry and biophysics	Biophysics (biological sciences)	53	39	57
Bioinformatics, biostatistics, and computational biology	Subtotal	136	169	196
Bioinformatics, biostatistics, and computational biology	Bioinformatics	70	82	101
Bioinformatics, biostatistics, and computational biology	Biometrics and biostatistics	32	32	44
Bioinformatics, biostatistics, and computational biology	Computational biology	34	55	51
Biology and biomedical sciences, general	Subtotal	248	251	287
Biology and biomedical sciences, general	Biological and biomedical sciences, general	127	141	170
Biology and biomedical sciences, general	Biomedical sciences	121	110	117
Biology and biomedical sciences, other	Subtotal	52	51	56
Biology and biomedical sciences, other	Biological and biomedical sciences, general	3	0	0
Biology and biomedical sciences, other	Biological and biomedical sciences, other	15	21	13
Biology and biomedical sciences, other	Biotechnology	3	2	5
Biology and biomedical sciences, other	Botany and plant biology	4	4	7
Biology and biomedical sciences, other	Entomology	0	3	2
Biology and biomedical sciences, other	Nutrition sciences	26	18	25
Biology and biomedical sciences, other	Plant genetics	0	1	2
Biology and biomedical sciences, other	Plant pathology/phytopathology (biological sciences)	0	1	1
Biology and biomedical sciences, other	Zoology	1	1	1
Cellular and developmental biology, and anatomy	Subtotal	75	82	75
Cellular and developmental biology, and anatomy	Anatomy	1	0	1
Cellular and developmental biology, and anatomy	Cell/cellular biology and histology	18	12	15
Cellular and developmental biology, and anatomy	Developmental biology and embryology	41	56	36
Cellular and developmental biology, and anatomy	Structural biology	15	14	23
Ecology, evolutionary biology, and epidemiology	Subtotal	112	132	128
Ecology, evolutionary biology, and epidemiology	Ecology	6	8	4
Ecology, evolutionary biology, and epidemiology	Epidemiology	98	117	114
Ecology, evolutionary biology, and epidemiology	Evolutionary biology	8	7	10
Genetics and genomics	Subtotal	161	172	180
Genetics and genomics	Genetics/genomics, human and animal	161	172	180
Microbiology and immunology	Subtotal	382	422	396
Microbiology and immunology	Bacteriology	4	4	10
Microbiology and immunology	Immunology	167	195	182

Field of Study: Broad and Major Category	Field of Study: Description	PhD FY: 2021	PhD FY: 2022	PhD FY: 2023
Microbiology and immunology	Microbiology	158	172	155
Microbiology and immunology	Parasitology	3	6	0
Microbiology and immunology	Virology	50	45	49
Molecular biology	Subtotal	258	280	304
Molecular biology	Molecular biology	258	280	304
Neurobiology and neurosciences	Subtotal	389	475	479
Neurobiology and neurosciences	Neurosciences and neurobiology	389	475	479
Pharmacology and toxicology	Subtotal	123	163	159
Pharmacology and toxicology	Environmental toxicology	8	9	7
Pharmacology and toxicology	Pharmacology, human and animal	88	115	120
Pharmacology and toxicology	Toxicology	27	39	32
Physiology, pathology, and cancer biology	Subtotal	200	235	230
Physiology, pathology, and cancer biology	Cancer biology	123	128	129
Physiology, pathology, and cancer biology	Endocrinology	3	0	2
Physiology, pathology, and cancer biology	Molecular medicine	18	19	20
Physiology, pathology, and cancer biology	Pathology, human and animal	13	28	28
Physiology, pathology, and cancer biology	Physiology, human and animal	43	60	51
Health sciences	**Overall**	**254**	**279**	**257**
Health sciences, other	Subtotal	79	107	90
Health sciences, other	Gerontology (health sciences)	1	1	2
Health sciences, other	Health sciences, general	1	2	1
Health sciences, other	Health sciences, other	14	29	21
Health sciences, other	Health systems administration	2	0	1
Health sciences, other	Kinesiology and exercise science	12	19	15
Health sciences, other	Medical physics/radiological science	10	16	13
Health sciences, other	Oral biology/oral pathology	4	6	3
Health sciences, other	Rehabilitation/therapeutic services	9	9	17
Health sciences, other	Speech-language pathology and audiology	26	25	17
Nursing science	Subtotal	62	49	47
Nursing science	Nursing science	62	49	47
Pharmaceutical sciences	Subtotal	28	34	36
Pharmaceutical sciences	Pharmaceutical sciences	28	34	36
Public health	Subtotal	85	89	84
Public health	Environmental health	21	15	20
Public health	Health and behavior	7	3	4
Public health	Health services research	11	14	6
Public health	Public health	46	57	54
Geosciences, atmospheric, and ocean sciences	**Overall**	**4**	**6**	**3**
Geological sciences	Subtotal	0	0	0
Geological sciences	Geological and earth sciences, general	0	0	0

Field of Study: Broad and Major Category	Field of Study: Description	PhD FY: 2021	PhD FY: 2022	PhD FY: 2023
Geological sciences	Geological and earth sciences, other	0	0	0
Geological sciences	Geology	0	0	0
Ocean, marine, and atmospheric sciences	Subtotal	4	6	3
Ocean, marine, and atmospheric sciences	Atmospheric chemistry and climatology	1	1	0
Ocean, marine, and atmospheric sciences	Hydrology and water resources	0	0	0
Ocean, marine, and atmospheric sciences	Marine biology and biological oceanography	3	5	3
Ocean, marine, and atmospheric sciences	Marine sciences	0	0	0
Physical sciences	**Overall**	**158**	**189**	**189**
Astronomy and astrophysics	Subtotal	1	3	1
Astronomy and astrophysics	Astronomy and astrophysics, other	1	0	0
Astronomy and astrophysics	Astrophysics	0	3	1
Chemistry	Subtotal	137	162	172
Chemistry	Analytical chemistry	17	26	13
Chemistry	Chemical biology	35	43	71
Chemistry	Chemistry, general	18	24	21
Chemistry	Chemistry, other	12	9	7
Chemistry	Inorganic chemistry	2	5	4
Chemistry	Medicinal chemistry	16	15	17
Chemistry	Organic chemistry	25	29	32
Chemistry	Physical chemistry	9	4	3
Chemistry	Polymer chemistry	1	2	0
Chemistry	Theoretical chemistry	2	5	4
Physics	Subtotal	20	24	16
Physics	Acoustics	0	0	0
Physics	Applied physics	1	5	0
Physics	Atomic/molecular/chemical physics	1	0	1
Physics	Biophysics (physics)	8	14	9
Physics	Condensed matter/low-temperature physics	0	0	0
Physics	Elementary particle physics	0	1	0
Physics	Nuclear physics	0	0	0
Physics	Optics/photonics	3	1	3
Physics	Physics, general	6	1	1
Physics	Physics, other	1	1	2
Physics	Plasma/high-temperature physics	0	1	0
Physics	Polymer physics	0	0	0
Mathematics and statistics	**Overall**	**24**	**28**	**19**
Applied mathematics	Subtotal	8	3	5
Applied mathematics	Applied mathematics	8	3	5
Mathematics	Subtotal	0	0	1
Mathematics	Topology/foundations	0	0	1
Mathematics and statistics, other	Subtotal	3	4	4

Field of Study: Broad and Major Category	Field of Study: Description	PhD FY: 2021	PhD FY: 2022	PhD FY: 2023
Mathematics and statistics, other	Mathematics/statistics, general	0	1	1
Mathematics and statistics, other	Mathematics/statistics, other	3	3	3
Statistics	Subtotal	13	21	9
Statistics	Statistics (mathematics)	13	21	9
Computer and information sciences	**Overall**	**14**	**17**	**17**
Computer and information sciences, other	Subtotal	4	5	7
Computer and information sciences, other	Computer and information sciences, general	2	0	0
Computer and information sciences, other	Computer and information sciences, other	2	5	7
Computer and information sciences, other	Information science and systems	0	0	0
Computer science	Subtotal	10	12	10
Computer science	Computer science	10	12	10
Psychology	**Overall**	**251**	**261**	**257**
Clinical psychology	Subtotal	112	94	114
Clinical psychology	Clinical psychology	112	94	114
Counseling and applied psychology	Subtotal	9	14	16
Counseling and applied psychology	Behavioral analysis	1	0	0
Counseling and applied psychology	Community psychology	0	2	1
Counseling and applied psychology	Counseling	4	4	4
Counseling and applied psychology	Educational psychology (psychology)	0	3	1
Counseling and applied psychology	Health and medical psychology	3	1	10
Counseling and applied psychology	Industrial and organizational psychology	1	1	0
Counseling and applied psychology	School psychology (psychology)	0	3	0
Psychology, other	Subtotal	28	36	32
Psychology, other	Human development and family studies	5	12	6
Psychology, other	Psychology, general	16	16	17
Psychology, other	Psychology, other	7	8	9
Research and experimental psychology	Subtotal	102	117	95
Research and experimental psychology	Cognitive neuroscience	58	72	52
Research and experimental psychology	Cognitive psychology and psycholinguistics	9	2	2
Research and experimental psychology	Developmental and child psychology	17	24	27
Research and experimental psychology	Experimental psychology	5	9	8
Research and experimental psychology	Neuropsychology/physiological psychology	7	4	0
Research and experimental psychology	Personality psychology	3	0	1
Research and experimental psychology	Psychometrics and quantitative psychology	0	0	0
Research and experimental psychology	Social psychology	3	6	5
Social sciences	**Overall**	**55**	**81**	**68**
Anthropology	Subtotal	9	10	10
Anthropology	Anthropology, cultural	4	1	2
Anthropology	Anthropology, general	0	0	1
Anthropology	Anthropology, physical and biological	5	9	7
Economics	Subtotal	6	7	9

Field of Study: Broad and Major Category	Field of Study: Description	PhD FY: 2021	PhD FY: 2022	PhD FY: 2023
Economics	Other economics	6	7	9
Political science and government	Subtotal	0	0	1
Political science and government	Political science and government	0	0	1
Public policy analysis	Subtotal	11	15	14
Public policy analysis	Health policy analysis	8	10	11
Public policy analysis	Public policy analysis	3	5	3
Social sciences, other	Subtotal	5	20	9
Social sciences, other	Area/ethnic/cultural studies	0	1	1
Social sciences, other	Criminal justice and corrections	0	0	1
Social sciences, other	Criminology	1	0	0
Social sciences, other	Geography	0	2	1
Social sciences, other	Gerontology (social sciences)	2	4	0
Social sciences, other	History, science and technology and society	0	2	1
Social sciences, other	Linguistics	2	5	2
Social sciences, other	Social sciences, general	0	3	0
Social sciences, other	Social sciences, other	0	2	2
Social sciences, other	Statistics (social sciences)	0	0	1
Social sciences, other	Urban, city, community and regional planning	0	1	0
Sociology, demography, and population studies	Subtotal	24	29	25
Sociology, demography, and population studies	Demography/population studies	3	4	4
Sociology, demography, and population studies	Sociology	21	25	21
Engineering	**Overall**	**309**	**338**	**332**
Aerospace, aeronautical, and astronautical engineering	Subtotal	0	1	1
Aerospace, aeronautical, and astronautical engineering	Mechanical engineering	0	1	1
Bioengineering and biomedical engineering	Subtotal	232	260	258
Bioengineering and biomedical engineering	Bioengineering and biomedical engineering	232	260	258
Chemical and petroleum engineering	Subtotal	32	41	31
Chemical and petroleum engineering	Chemical engineering	31	41	31
Chemical and petroleum engineering	Polymer and plastics engineering	1	0	0
Civil, environmental, and transportation engineering	Subtotal	7	5	3
Civil, environmental, and transportation engineering	Civil engineering	1	4	1
Civil, environmental, and transportation engineering	Environmental/environmental health engineering	6	1	2
Electrical and computer engineering	Subtotal	8	5	7
Electrical and computer engineering	Computer engineering	1	1	0
Electrical and computer engineering	Electrical, electronics and communications engineering	7	4	7

Field of Study: Broad and Major Category	Field of Study: Description	PhD FY: 2021	PhD FY: 2022	PhD FY: 2023
Engineering, other	Subtotal	9	6	10
Engineering, other	Engineering science	2	1	0
Engineering, other	Engineering, general	0	0	1
Engineering, other	Engineering, other	7	5	8
Engineering, other	Nuclear engineering	0	0	1
Industrial engineering and operations research	Subtotal	2	2	1
Industrial engineering and operations research	Industrial and manufacturing engineering	2	0	0
Industrial engineering and operations research	Operations research (engineering)	0	1	0
Industrial engineering and operations research	Systems engineering	0	1	1
Materials and mining engineering	Subtotal	6	5	3
Materials and mining engineering	Materials science engineering	6	5	3
Mechanical engineering	Subtotal	13	13	18
Mechanical engineering	Mechanical engineering	12	12	17
Mechanical engineering	Robotics	1	1	1
Other Fields	**Overall**	**25**	**20**	**34**
NIH Total	**Grant Total**	**3,461**	**3,910**	**3,942**

Table 7. Demographic Characteristics of NRSA Participants[1524]

Demographic Characteristic	FY 2021	FY 2022	FY 2023
Sex			
Female	57.5%	57.8%	58.1%
Male	39.3%	38.5%	37.3%
Unknown	3.2%	3.6%	4.6%
Withheld	0.0%	0.0%	0.0%
Race			
White	62.1%	60.6%	59.0%
Asian	15.9%	16.3%	17.3%
Black or African American	8.4%	8.6%	8.5%
American Indian or Alaska Native	0.8%	0.7%	0.7%
Native Hawaiian or Other Pacific Islander	0.2%	0.1%	0.1%
Person Reporting More Than one Race	5.5%	5.7%	5.8%
Withheld	6.2%	5.5%	5.1%

[1524] NRSA Training grants are T32, T34, T35, T90, TL1, TL4, and TU2. Fellowship grants are F30, F31, F32, and F33. TL4 trainees were included beginning in 2015. Data were drawn from IMPAC II Current Files as of 06/05/2025 and are subject to change. Sex, race, and ethnicity are self-reported. CTSA trainees are included in the NRSA data provided.

Demographic Characteristic	FY 2021	FY 2022	FY 2023
Sex			
Unknown	1.0%	2.4%	3.3%
Ethnicity			
Hispanic or Latino	14.2%	15.0%	16.0%
Not Hispanic or Latino	82.2%	81.4%	80.5%
Unknown	3.6%	3.6%	3.5%
Withheld	0.0%	0.0%	0.0%

Table 8. Successfully Completed Residency and Subspecialty Training by Academic Year

NIH Clinical Center Program Specialty	Completed 2021/2022	Completed 2022/2023	Completed 2023/2024
Allergy and Immunology	4	4	4
Blood Banking/Transfusion Medicine	3	3	3
Critical Care Medicine	2	4	6
Cytopathology	1	0	1
Endocrinology, Diabetes, and Metabolism	4	3	4
Hematopathology	2	2	2
Hematology-Oncology	13	13	9
Hospice and Palliative Medicine	2	2	2
Infectious Disease	5	4	2
Laboratory Genetics and Genomics	7	5	6
Medical Biochemical Genetics	3	2	1
Medical Genetics and Genomics	5	4	2
Neurological Surgery	1	1	0
Pathology (Anatomic and Clinical)	3	3	2
Clinical Biochemical Genetics	0	2	2
Pediatric Endocrinology	1	1	1
Psychiatry	2	3	3
Reproductive Endocrinology	3	4	4
Rheumatology	2	1	2
Vascular Neurology	1	3	2
Total	**64**	**64**	**58**

Appendix F: Monitoring Adherence to the NIH Policy and Guidelines on the Inclusion of Women and Minorities in Clinical Research

All NIH-funded studies that meet the NIH definition for clinical research are required by law to address plans for the inclusion of women and minorities within the application or proposal in a manner that is appropriate to the scientific question under study.[1525] NIH has examined and reported aggregate inclusion enrollment information for its portfolio of NIH-funded clinical research since FY94. These reports are one component of the NIH policy on the Inclusion of Women and Minorities in Clinical Research.

For each NIH IC that supports clinical research, triennial reports on inclusion have been produced with all NIH enrollment information for FY22 to FY24.

An NIH-wide report covering FY21 to FY22, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, is published as part of the *Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2021 – 2022 (starting on page 36).*[1526]

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#/

Data on enrollment by age are also available at the above link.

[1525] https://grants.nih.gov/policy-and-compliance/policy-topics/inclusion/women-and-minorities

[1526] https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Biennial%20Report_121823_1516_F_508c_Optimized.pdf

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 maintains a list of NIH-supported data repositories[1527] 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[1528] works across NIH to modernize the data repository ecosystem to support the storage and sharing of data and to standardize data and adopt common data elements.[1529]

NIH exemplifies and promotes the highest level of public accountability and transparency. To that end, the Research Portfolio Online Reporting Tools (RePORT)[1530] 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[1531] (RePORT Expenditures and Results) module. RePORTER is a publicly accessible 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,[1532] which summarizes the most commonly asked questions about the NIH budget and extramural programs. Another tool is called Awards by Location,[1533] which summarizes NIH awards for a particular fiscal year by the location and organization of the awardees. The categorical spending tool[1534] displays the annual funding level for various research, condition, and disease categories based on grants, contracts, and other funding mechanisms used across NIH, as well as select disease burden data.

[1527] https://www.nlm.nih.gov/NIHbmic/index.html
[1528] https://datascience.nih.gov/data-ecosystem
[1529] https://datascience.nih.gov/fhir-initiatives/common-data-elements
[1530] https://report.nih.gov/
[1531] https://reporter.nih.gov/
[1532] https://report.nih.gov/nihdatabook/
[1533] https://report.nih.gov/award/index.cfm
[1534] https://report.nih.gov/funding/categorical-spending#/

Appendix H: Actions Undertaken to Carry Out Scientific Frameworks on Recalcitrant Cancer

Update on Progress including Pancreatic Ductal Adenocarcinoma and Small Cell Lung Cancer Activities, FY22 to FY24

As required by the *Recalcitrant Cancer Research Act (RCRA) of 2012*, 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 Pancreatic Ductal Adenocarcinoma (PDAC) and Small Cell Lung Cancer (SCLC). The frameworks were adopted by NCI's Clinical Trials and Translational Research Advisory Committee and informed by the assessments of the scientific and clinical leaders who participated in Committee working groups. The frameworks were finalized in 2014 and reviewed in 2019.[1535] 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.

PDAC framework priorities

To address the PDAC framework priorities, NCI leveraged existing research efforts, including NCI's Early Detection Research Network,[1536] the NCI RAS Initiative,[1537] and the RAS Synthetic Lethality Network. NCI formed three new programs: PDAC as it relates to immunotherapy, early detection,[1538] and diabetes and pancreatitis (in collaboration with NIDDK), which was reissued in 2019. In FY22 to FY24, 20 research awards were funded in response to three PDAC Consortium Notice of Funding Opportunities (NOFOs). Additionally, between FY22 and FY24, there were 25 active NCI clinical trials for patients with PDAC. NCI has maintained support for Specialized Programs of Research Excellence (SPOREs), including research on pancreatic cancer and two gastrointestinal cancer SPOREs that have a PDAC focus.[1539]

[1535] https://deainfo.nci.nih.gov/advisory/ctac/workgroup/ctacsupmat.htm
[1536] https://edrn.nci.nih.gov/
[1537] https://www.cancer.gov/research/key-initiatives/ras
[1538] https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection-consortium
[1539] https://trp.cancer.gov/spores/abstracts/dfhcc_gi.htm

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, including development of a biomarker panel to potentially identify patients with early-stage PDAC.[1540]

SCLC framework priorities

To address the SCLC framework priorities, NCI launched and continues to support the SCLC Consortium. In 2019, NCI reissued the NOFO (expired in March 2022) focused on new therapy and drug resistance projects and extended the scope to research in SCLC biology.[1541] During FY22 to FY24, NCI supported 19 research projects and one coordinating center. From 2022 to 2024, there were 36 active clinical trials for SCLC patients. Additionally, two of the eight NCI Lung SPOREs have a focus on SCLC.[1542]

PDAC and SCLC NOFOs from FY22, FY23, and FY24

Below are PDAC and SCLC NOFOs from FY22 to FY24. The tables 10 and 11 contain a full list of all NIH-supported PDAC and SCLC research projects for FY22 to FY24.

NOFOs related to Small-Cell Lung Cancer released or active in FY22 to FY24:

- PAR-21-346 (posted Sept 2021, opened Oct 2021): Limited Competition: Coordinating Center for the Small Cell Lung Cancer Consortium (U24 Clinical Trial Not Allowed)[1543]

NOFOs related to Pancreatic Ductal Adenocarcinoma released or active in FY22 to FY24:

- RFA-CA-21-041 (posted July 2021, opened Oct 2021): Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium (U01 Clinical Trial Not Allowed)[1544]
- RFA-CA-21-042 (posted July 2021, opened Oct 2021): Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium Coordinating and Data Management Center (U24 Clinical Trial Not Allowed)[1545]
- PAR-21-334 (posted Sept 2021, opened Oct 2021): Pancreatic Cancer Detection Consortium: Research Units (U01 Clinical Trial Optional)[1546]
- PAR-21-335 (posted Sept 2021, opened Oct 2021): Pancreatic Cancer Detection Consortium: Management and Data Coordination Unit (U24 Clinical Trial Not Allowed)[1547]

FY22, FY23, and FY24 NIH Projects Related to PDAC

[1540] Xu C, et al. Gastroenterology. 2024 Jan;166(1):178-190.e16. Epub 2023 Oct 14. PMID: 37839499.
[1541] https://grants.nih.gov/grants/guide/pa-files/PAR-19-361.html
[1542] trp.cancer.gov/spores/abstracts/fhcrc_lung.htm
[1543] https://grants.nih.gov/grants/guide/pa-files/PAR-21-346.html
[1544] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-041.html
[1545] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-042.html
[1546] https://grants.nih.gov/grants/guide/pa-files/PAR-21-334.html
[1547] https://grants.nih.gov/grants/guide/pa-files/PAR-21-335.html

Table 10: FY22, FY23, and FY24 NIH Projects Related to PDAC

Project Number	Title	Principal Investigator(s)	Institution
2682017000006I-0-759202300004-1	CIDR - Genotyping Services Using Illumina Human Methylation Epic Array Version 2 (BLOOD) On 1,495 Experimental DNA Samples, NCI, Huang	KIMBERLY F DOHENY	JOHNS HOPKINS UNIVERSITY
75N91019D00021-0-759102100003-1	TASK ORDER TITLE: EVALUATION OF REAL-TIME METABOLIC IMAGING BIOMARKERS FOR DETECTION OF PANCREATIC PREMALIGNANT LESIONS	POWELL BROWN	UNIVERSITY OF TX MD ANDERSON CAN CTR
75N91019D00021-0-759102300003-1	Targeting the A2B Adenosine Receptor for Immunoprevention of Pancreatic Cancer	XIANGWEI WU	UNIVERSITY OF TX MD ANDERSON CAN CTR
75N91023C00015-0-9999-1	Purpose Of This Modification Is To Exercise The I-CORP Option	EHSAN YAZDI	NOMOCAN PHARMACEUTICALS, LLC
ACN21007002-2-0-1	NCI Early Detection Research Network: Biomarker Reference and Resource Center (BRRC)		NATIONAL CANCER INSTITUTE
ACN23011001-1-0-1	NCI Early Detection Research Network: Biomarker Reference and Resource Center (BRRC)		NATIONAL CANCER INSTITUTE
DP2CA228042	Dissecting tumor metabolic heterogeneity *in vivo*	KIVANC BIRSOY	ROCKEFELLER UNIVERSITY
DP2CA271386	Innovations and mechanisms in tumor subcellular metabolism	MONTHER ABU-REMAILEH	STANFORD UNIVERSITY
DP2CA290967	Optogenetic engineering of tumor topography in native tissue environments	RAVIKANTH MADDIPATI	UT SOUTHWESTERN MEDICAL CENTER
DP2CA301099	Novel Strategies to Enhance Drug Delivery and Tumor Immunogenicity in Pancreatic Cancer	BOLNI MARIUS NAGALO	UNIV OF ARKANSAS FOR MED SCIS
DP5OD026427	Immune Activating CAR-Modified Antigen Presenting Cells	CARL DESELM	WASHINGTON UNIVERSITY
DP5OD031864	Cellular phenotypic heterogeneity and resistance to radiotherapy in pancreatic adenocarcinoma	KENNETH L PITTER	OHIO STATE UNIVERSITY
F30CA228258	The Role of Mutant p53 in Regulating T-cell Immune Evasion in Pancreatic Adenocarcinoma and Other Cancers	DEBORAH ANN SILVERMAN	UNIVERSITY OF TX MD ANDERSON CAN CTR
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 SCHOOL OF MEDICINE
F30CA243233	Elucidating the protective role of stromal fibrosis to radiation-induced tumor immunity	VARINTRA EDLYN LANDER	WASHINGTON UNIVERSITY
F30CA243253	Validation of WEE1 kinase as a clinical target in KRAS-mutant pancreatic cancer	JOHN NATHANIEL DIEHL	UNIV OF NORTH CAROLINA CHAPEL HILL
F30CA254033	The Role of Lipocalin 2 in Cancer Cachexia	BRENNAN GLENN OLSON	OREGON HEALTH & SCIENCE UNIVERSITY

Project Number	Title	Principal Investigator(s)	Institution
F30CA254087	Harnessing Dendritic Cells as a Novel Therapy in Pancreatic Ductal Adenocarcinoma	GRAHAM DOUGLAS HOGG	WASHINGTON UNIVERSITY
F30CA257287	Dysregulation of Liver Macrophages in Pancreatic Cancer	STACY KATHERINE THOMAS	UNIVERSITY OF PENNSYLVANIA
F30CA257489	Single Cell Deconvolution of the Pancreatic Tumor Microenvironment	KI OH	STATE UNIVERSITY NEW YORK STONY BROOK
F30CA260944	Identifying the Role of Tumor Cell Intrinsic DNMT1 in Anti-Tumor Immunity in Pancreatic Ductal Adenocarcinoma	ERIN ELIZABETH HOLLANDER	UNIVERSITY OF PENNSYLVANIA
F30CA265134	Characterizing the biochemistry and dynamics of the immune suppressive CXCL12 coat in pancreatic cancer	PHILIP ANDREW MORESCO	STATE UNIVERSITY NEW YORK STONY BROOK
F30CA265277	Targeting pyrimidine biosynthesis in pancreatic ductal adenocarcinoma	NICHOLAS JAMES MULLEN	UNIVERSITY OF NEBRASKA MEDICAL CENTER
F30CA278322	Anti-Complement Immunotherapy for Pancreatic Cancer	BRETT I BELL	ALBERT EINSTEIN COLLEGE OF MEDICINE
F30CA284534	Investigating tRNA biology as a prognostic and oncogenic feature in pancreatic adenocarcinoma	RYAN KAWALERSKI	JOHNS HOPKINS UNIVERSITY
F30CA291094	Investigating the MAIT cell- Microbiome Relationship in Pancreatic Cancer Liver Metastasis	JUGMOHIT TOOR	WAYNE STATE UNIVERSITY
F30CA291095	The role of CCR6 in Pancreatic Cancer and Tregs	DONOVAN G DROUILLARD	MEDICAL COLLEGE OF WISCONSIN
F30CA294875	Promoting Activated Natural Killer (NK) Cell Accumulation in Pancreatic Cancer	ALEXANDER LEKAN	GEORGETOWN UNIVERSITY
F30HL170476	The role of adrenergic signaling in cancer cachexia-associated cardiac remodeling	PARHAM DIBA	OREGON HEALTH & SCIENCE UNIVERSITY
F31CA235997	Bioresponsive MR probes for imaging pancreatic cancer	MEGAN KASTER	NORTHWESTERN UNIVERSITY
F31CA243344	Metabolism of Extracellular Matrix Supports Pancreatic Cancer Growth	PETER KIM	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA246901	Single Cell Dissection of Epigenetic and Tumor Ecosystem Dynamics During Pancreatic Cancer Progression	CASSANDRA BURDZIAK	WEILL MEDICAL COLL OF CORNELL UNIV
F31CA247037	Elucidating Kras-driven immune infiltration and function in pancreatic cancer	ASHLEY VELEZ	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA247257	Regulation of inhibitory DAMP to harness immunogenic cell death	KAZUKUNI HAYASHI	CEDARS-SINAI MEDICAL CENTER
F31CA247416	Elucidating fibroblast/immune crosstalk and plasticity in pancreatic ductal adenocarcinoma	JENNIFER SUSAN THALAPPILLIL	STATE UNIVERSITY NEW YORK STONY BROOK
F31CA247489	Defining the role of chromatin remodeling complexes in pancreatic cancer stem cells	LESLEY PAIGE FERGUSON	UNIVERSITY OF CALIFORNIA, SAN DIEGO
F31CA247527	Mechanistic Insights and Diagnostic Applications for Hypoxia-Induced Vasorin in Pancreatic Cancer	LISA KIRKEMO	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Project Number	Title	Principal Investigator(s)	Institution
F31CA250135	T cell mechanisms of immunotherapy response in pancreatic ductal adenocarcinoma	EMILY DAVIS	JOHNS HOPKINS UNIVERSITY
F31CA250353	Synthesis, and Evaluation of Potent and Selective MEK4 Inhibitors as a Targeted Therapeutic for Metastatic Pancreatic Ductal Adenocarcinoma	ADA JADE KWONG	NORTHWESTERN UNIVERSITY
F31CA250443	Bacterial Delivery of CXCR7 Nanobodies to Alleviate Immune Suppression in Pancreatic Cancer	AMANDA ROSE DECKER-FARRELL	COLUMBIA UNIVERSITY HEALTH SCIENCES
F31CA250489	The transcriptional and epigenetic landscape of cell fate changes in murine pancreatic cancer initiation and metastasis	EMILY LO	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	UNIV OF NORTH CAROLINA CHAPEL HILL
F31CA257533	Myeloid cell driven immune suppression in pancreatic cancer	ROSA ELENA MENJIVAR	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA260796	Genetic Determinants of Evolutionary Trajectories and Clinical Course in Pancreatic Cancer	KATELYN MULLEN	SLOAN-KETTERING INST CAN RESEARCH
F31CA260942	Impact of benzodiazepines on the pancreatic tumor microenvironment	ABIGAIL CARISSA CORNWELL	ROSWELL PARK CANCER INSTITUTE CORP
F31CA261041	The role of branched-chain amino acid metabolism and hyperinsulinemia in pancreatic cancer	MICHAEL NOJI	UNIVERSITY OF PENNSYLVANIA
F31CA261044	Tumor-Specific Nanocontrast Agents for Improved Detection of Pancreatic Cancer	WILLIAM MACCUAIG	UNIVERSITY OF OKLAHOMA
F31CA261124	Mechanisms regulating the formation of a pro-metastatic niche and tumor cell dormancy in the liver	JESSE LEE	UNIVERSITY OF PENNSYLVANIA
F31CA261125	Pancreatic Stellate Cell (PSC) Engagement of Natural Killer (NK) cells in the Pancreatic Ductal Adenocarcinoma (PDAC) Tumor Microenvironment	ZOE XENOS MALCHIODI	GEORGETOWN UNIVERSITY
F31CA265085	Regulation and role of fibroblast-derived interleukin-33 in the pancreatic tumor microenvironment	KATELYN LOIS DONAHUE	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA265166	Inflammation-induced cellular plasticity in pancreatic homeostasis and tumorigenesis	DAVID FALVO	WEILL MEDICAL COLL OF CORNELL UNIV
F31CA265168	The Role of Oncostatin M in the PDAC tumor microenvironment and macroenvironment	DAENIQUE JENGELLEY	INDIANA UNIVERSITY INDIANAPOLIS
F31CA265173	Differential pathway engagement and the biological consequences of KRAS variants in cancer	YANIXA QUINONES AVILES	YALE UNIVERSITY

Project Number	Title	Principal Investigator(s)	Institution
F31CA268724	Determining Dendritic Cell Responses to Vaccine-based Immunotherapy in PDAC at Single Cell Resolution.	DIMITRIOS N SIDIROPOULOS	JOHNS HOPKINS UNIVERSITY
F31CA268835	Comprehensive modeling of tumor suppressor gene-derived neoantigens in pancreatic cancer	ZACKERY ELY	MASSACHUSETTS INSTITUTE OF TECHNOLOGY
F31CA271576	Understanding the Fate of Metaplastic Tuft Cells in the Progression of Pancreatic Cancer	DANIEL JAMES SALAS-ESCABILLAS	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA271692	A Role for TLR2 in Regulating Immune Surveillance in Pancreatic Ductal Adenocarcinoma	JACQUELINE PLESSET	UNIVERSITY OF PENNSYLVANIA
F31CA271724	Oncogenic insults within the pancreatic ductal glands produce pre-malignant lesions and PDAC	KYLE MCANDREWS	UNIVERSITY OF NEBRASKA MEDICAL CENTER
F31CA275096	Defining the Mitotic Role of Chk2 for the Treatment of Pancreatic Cancer	ELIZABETH MAUREEN BLACK	YALE UNIVERSITY
F31CA275260	Mechanisms of YAP1-driven resistance to KRAS-G12C inhibition	ALEXANDER COLE EDWARDS	UNIV OF NORTH CAROLINA CHAPEL HILL
F31CA275289	Elucidating the Role of Tregs in Cancer Metastasis and T Cell Dysfunction	ZOE SCHMIECHEN	UNIVERSITY OF MINNESOTA
F31CA275364	Assessing the Transcriptional and Signaling Basis of Heterogeneity in the Epithelial-Mesenchymal Transition in Pancreatic Ductal Adenocarcinoma	MICHELLE C BARBEAU	UNIVERSITY OF VIRGINIA
F31CA278362	Role of PDK1 in pancreatic cancer cell fitness under tumor nutrient stress	COLIN SHEEHAN	UNIVERSITY OF CHICAGO
F31CA278589	Role of Gastrokine 2 in pancreatic cancer development	WHITNEY JEAN BELL	UNIV OF NORTH CAROLINA CHAPEL HILL
F31CA278591	Targeting of Krüppel-like Factor 5 (KLF5) in Pancreatic Ductal Adenocarcinoma	PATRICK CUNNIFF	COLD SPRING HARBOR LABORATORY
F31CA281079	Role of hypoxia in CD8+ T cell exclusion and suppression in pancreatic cancer	ASHLEY MELLO	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA281118	Investigating the role of SHP2-PLCG1 interaction in PDAC calcium signaling and metabolism	RICHARD MCKINNON WALSH	UNIVERSITY OF KANSAS MEDICAL CENTER
F31CA281194	Hypoxic regulation of macrophage migration and function via fibroblast reprogramming in pancreatic cancer	SEAN MATTHEW HANNIFIN	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA281241	Defining cell intrinsic and extrinsic regulators of ferroptosis in pancreatic cancer	HEATHER MARIE GIZA	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA281246	The impact of sepsis-induced inflammation on pancreatic cancer liver metastasis	NICOLE SIVETZ	COLD SPRING HARBOR LABORATORY
F31CA284505	The role of mesothelial-derived cancer-associated fibroblasts in the pathogenesis of pancreatic ductal adenocarcinoma	ALLISON BISCHOFF	UNIVERSITY OF MICHIGAN AT ANN ARBOR

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F31CA284520	Role of hypoxia in fibroblast reprogramming in pancreatic cancer	TENZIN NGODUP	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F31CA284525	Investigation of Immunotherapy-induced Alterations to Cellular Communication Networks in Pancreatic Ductal Adenocarcinoma	JACOB THOMAS MITCHELL	JOHNS HOPKINS UNIVERSITY
F31CA284869	Mechanistic examination and inhibitor targeting of nutrient scavenging for the treatment of pancreatic cancer	RYAN ROBB	UNIV OF NORTH CAROLINA CHAPEL HILL
F31CA287966	Defining novel functions of ATF4 in early stages of pancreatic cancer tumorigenesis	LEAH MARIE ZIOLKOWSKI	UNIVERSITY OF CHICAGO
F31CA288079	Defining the role of the mitochondrial protein, GOT2, in pancreatic cancer metastasis and epigenetic dysregulation	LUIS FRANCISCO DIAZ	OREGON HEALTH & SCIENCE UNIVERSITY
F31CA288132	Understanding Kras Mutation Heterogeneity in PDAC	WHITNEY JULIET SISSO	WEILL MEDICAL COLL OF CORNELL UNIV
F31CA288141	Defining Novel Redox Stress Mechanisms to Inhibit KRAS-driven Pancreatic Ductal Adenocarcinoma	BEATRIZ MATEO-VICTORIANO	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
F31CA291031	Investigating the role of FOXA1/2 and HNF4α in Pancreatic ductal adenocarcinoma	WALTER ALEXANDER ORELLANA	UNIVERSITY OF UTAH
F31CA294908	A novel immunotherapy for pancreatic cancer using micro-RNA-29a	CHRISTINE ISABELLE RAFIE	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
F31CA294972	Engineering CD4+ T cells to develop a novel immunotherapy for pancreatic cancer	DELANEY KATE GEITGEY	EMORY UNIVERSITY
F31DE033887	Divergent response to radio-immunotherapy in HNSCC and PDAC is mediated by regulatory T cells	JACOB GADWA	UNIVERSITY OF COLORADO DENVER
F31DK122633	Investigating the relationship between macrophage ontogeny and function during pancreatitis	JOHN M BAER	WASHINGTON UNIVERSITY
F32CA232529	Defining the contributions of WT RAS in RAS-mutant lung cancer	CLINT A STALNECKER	UNIV OF NORTH CAROLINA CHAPEL HILL
F32CA232543	The novel PRMT5-substrate adaptor interface provides a therapeutic target in MTAP null tumors	KATHLEEN MULVANEY	BROAD INSTITUTE, INC.
F32CA239417	Characterizing and Targeting the Hypoxic T Cell Surfaceome to Promote Immune Function in Cancer	JAMES ROBERT 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 INST
F32CA247492	Defining and Targeting Malic Enzyme Dependence in Pancreatic Cancer	MENGROU SHAN	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F32CA250144	The Mitochondrial Calcium Uniporter in Pancreatic Cancer Development, Metastasis, and Treatment	JILLIAN WEISSENRIEDER	UNIVERSITY OF PENNSYLVANIA

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F32CA250190	Modulating one-carbon metabolism with diet and targeted inhibitors to treat cancer	MATTHEW JOSEPH MCBRIDE	PRINCETON UNIVERSITY
F32CA260118	Effects of GPCR trafficking on the spatiotemporal control of signaling	EMILY ELIZABETH BLYTHE	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
F32CA264906	ST6Gal-1 contributes to pancreatic cancer initiation by promoting pancreatitis-induced acinar to ductal metaplasia	MICHAEL MARCIEL	UNIVERSITY OF ALABAMA AT BIRMINGHAM
F32CA265042	Elucidating the molecular mechanisms of PRMT5i response and resistance in LUAD and PDAC	PEDRO NICOLAS POZO	MASSACHUSETTS INSTITUTE OF TECHNOLOGY
F32CA265052	The role of sympathetic nerve associated macrophages during pancreatic adenocarcinoma progression	JONATHAN ROBERT WEITZ	UNIVERSITY OF CALIFORNIA, SAN DIEGO
F32CA268912	Understanding tumorigenesis and metastasis of pancreatic cancer through precision whole-body imaging of senescence with ImmunoPET	EDWIN CHARLES PRATT	SLOAN-KETTERING INST CAN RESEARCH
F32CA271470	Structural modeling of neoantigen presentation for rational design of heteroclitic neoepitope vaccines	AMANDA L HUFF	JOHNS HOPKINS UNIVERSITY
F32CA275283	Metabolic pathways regulate metaplasia and cancer initiation in the pancreas	MEGAN DEANNA RADYK	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F32CA284723	Exploring the molecular mechanisms controlling CDK7i sensitivity in pancreas cancer	ADRIANNE WALLACE-POVIRK	FRED HUTCHINSON CANCER CENTER
F99CA264414	Reprogramming Metabolic Networks in the Tumor Microenvironment	SAMUEL ANDREW KERK	UNIVERSITY OF MICHIGAN AT ANN ARBOR
F99CA264434	Understanding Memory T-Cell responses to cancer and the role of microbiome.	JICHANG HAN	DARTMOUTH COLLEGE
F99CA284259	Mechanisms of gene expression regulation in pancreatic cancer	DAVID R PEASE	MAYO CLINIC ROCHESTER
F99CA284289	Chromatin and immune regulation of tumor growth and progression	EMILY LORIN ASHKIN	STANFORD UNIVERSITY
F99CA284292	Immune Regulation of Dormancy at the Metastatic Site	XIAO HAN	STATE UNIVERSITY NEW YORK STONY BROOK
F99CA284365	Real Time Metabolic Imaging to Interrogate Early Detection and Prevention of Pancreatic Cancer	JOSE S ENRIQUEZ	UNIVERSITY OF TX MD ANDERSON CAN CTR
F99CA294132	The Role of Guanine Exchange Factors in Pancreatic Ductal Adenocarcinoma (PDAC)	SAHAR BANNOURA	WAYNE STATE UNIVERSITY
K00CA212451	The role of neutrophils in pancreatic cancer pre-metastatic and metastatic niche formation	SAMER HANNA	WEILL MEDICAL COLL OF CORNELL UNIV
K00CA223043	Defining the barriers to immune surveillance in solid tumors	SAMARTH HEGDE	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

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K00CA234962	Pancreatic cancer stem cells: PD2-mediated novel mechanistic link and metabolomic alterations	SASWATI KARMAKAR	STANFORD UNIVERSITY
K00CA245822	Identifying Metabolic Vulnerabilities in Pancreatic Cancer	DOUGLAS BIANCUR	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
K00CA253718	Deciphering molecular mechanisms of Epithelial Plasticity	EMILY NICOLE ARNER	VANDERBILT UNIVERSITY MEDICAL CENTER
K00CA264414	Reprogramming Metabolic Networks in the Tumor Microenvironment	SAMUEL ANDREW KERK	SALK INSTITUTE FOR BIOLOGICAL STUDIES
K00CA264434	Deciphering the role of tumor-macrophage crosstalk during metastatic dissemination to the peritoneum	JICHANG HAN	WASHINGTON UNIVERSITY
K01CA240533	Training and Research on Mechanisms of Pancreatic Cancer Associated Muscle Wasting and Related Therapies	CALVIN LLOYD COLE	UNIVERSITY OF ROCHESTER
K07CA222159	Obesity and Pancreatic Cancer Progression and Survival	ANA BABIC	DANA-FARBER CANCER INST
K08CA218420	Functional interrogation of epigenetic vulnerabilities in KRAS-mutant pancreatic cancer	ANDREW JAMES AGUIRRE	DANA-FARBER CANCER INST
K08CA218690	Defining diverse roles of p53 in pancreatic cancer	MICHAEL PAUL KIM	UNIVERSITY OF TX MD ANDERSON CAN CTR
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-β signaling in pancreatic cancer	JIAQI SHI	UNIVERSITY OF MICHIGAN AT ANN ARBOR
K08CA241084	Immune Evasion in Pancreatic Cancer	MARK STEPHEN DIAMOND	UNIVERSITY OF PENNSYLVANIA
K08CA241341	Investigating the non-cell autonomous immune effects of mutant p53 in pancreatic cancer	DESPINA SIOLAS	WEILL MEDICAL COLL OF CORNELL UNIV
K08CA245188	Hepatic metabolic reprogramming drives pancreatic cancer cachexia	AARON GROSSBERG	OREGON HEALTH & SCIENCE UNIVERSITY
K08CA248473	Cost Effectiveness of Germline Genetic Testing in Pancreatic Cancer	MARY LINTON B PETERS	BETH ISRAEL DEACONESS MEDICAL CENTER
K08CA248624	Neoantigen-Targeted Vaccines in Combination with Immune Checkpoint Inhibitors for Pancreatic Cancer	NEEHA ZAIDI	JOHNS HOPKINS UNIVERSITY
K08CA248710	Personalized preclinical models in pancreas cancer: a tractable approach to precision medicine	RICHARD ANDREW BURKHART	JOHNS HOPKINS UNIVERSITY
K08CA259456	Targeting the Stroma for Pancreatic Cancer Treatment	ARSEN OSIPOV	CEDARS-SINAI MEDICAL CENTER
K08CA259610	Developing novel CAR T cell designs using combinatorial antigen detection	GREG MANESS ALLEN	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
K08CA259621	Elucidating the molecular and cellular mechanisms of immune evasion in pancreatic cancer	WILLIAM A FREED-PASTOR	DANA-FARBER CANCER INST

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K08CA259626	Molecular Imaging of Fibrosis for Improved Treatment Planning of Pancreatic Ductal Adenocarcinoma	SHADI ABDAR ESFAHANI	MASSACHUSETTS GENERAL HOSPITAL
K08CA260442	Regulation and targeting of tumor cell states and plasticity in pancreatic cancer	SRIVATSAN RAGHAVAN	DANA-FARBER CANCER INST
K08CA270417	Elucidating cancer-intrinsic mechanisms of perineural invasion in pancreatic cancer	WILLIAM L HWANG	MASSACHUSETTS GENERAL HOSPITAL
K08CA277009	Investigating CD4+ T cell memory in cancer immunotherapy	MAX WATTENBERG	UNIVERSITY OF PENNSYLVANIA
K08CA282374	Microbial Dysbiosis in Pancreatic Cancer Initiation and Progression	DONNELE DALEY	UNIVERSITY OF MICHIGAN AT ANN ARBOR
K08CA282968	Lung fibrosis impairs tumor immunity and limits immune checkpoint efficacy	BRETT HOWARD HERZOG	WASHINGTON UNIVERSITY
K08CA286749	Improving response prediction to neoadjuvant therapy in pancreatic cancer	HARSHABAD SINGH	DANA-FARBER CANCER INST
K08DK122130	Tissue Resident Immune Cells in Human Pancreas.	STUART P WEISBERG	COLUMBIA UNIVERSITY HEALTH SCIENCES
K22CA237620	The role of PP2A B56a in pancreatic tumorigenesis	BRITTANY ALLEN-PETERSEN	PURDUE UNIVERSITY
K22CA241387	Imaging zinc secretion from the exocrine pancreas for the early diagnosis of pancreatic adenocarcinoma with MRI	MARIA VERONICA CLAVIJO JORDAN	MASSACHUSETTS GENERAL HOSPITAL
K22CA251491	Tumor-TAMs crosstalk enables bypass of oncogenic KRAS dependency in pancreatic cancer	PINGPING HOU	RUTGERS BIOMEDICAL AND HEALTH SCIENCES
K22CA251643	Contribution of the Inflammasome to Radiation Response in Pancreatic Cancer	TERRY R MEDLER	PROVIDENCE PORTLAND MEDICAL CENTER
K22CA258805	Targeted disruption of the YAP/TAZ/TEAD axis in pancreatic cancer	BEHNAM NABET	FRED HUTCHINSON CANCER CENTER
K22CA276360	Unraveling the functional contribution of extracellular vesicles in pancreatic cancer	KATHLEEN MCANDREWS	UNIVERSITY OF TX MD ANDERSON CAN CTR
K22CA276632	Identification of resistance mechanisms to direct KRAS inhibition in pancreatic cancer	ANDREW M WATERS	UNIVERSITY OF CINCINNATI
K25CA267052	Early Detection of Pancreatic Cancer with Human-in-the-Loop Deep Learning	JIHEUM PARK	COLUMBIA UNIVERSITY HEALTH SCIENCES
K99CA229979	Experimental evolution of pancreatic cancer	ALVIN MAKOHON-MOORE	SLOAN-KETTERING INST CAN RESEARCH
K99CA248495	Interrogating the RAS interactome for therapeutic vulnerabilities	HEMA ADHIKARI	DUKE UNIVERSITY
K99CA252009	Function of mesothelial cells in the tumor microenvironment of pancreatic ductal adenocarcinoma	HUOCONG HUANG	UT SOUTHWESTERN MEDICAL CENTER
K99CA252153	Dissecting the oncogenic and pro-metastatic roles of PTHLH-mediated calcium signaling in pancreatic cancer	JASON R. PITARRESI	UNIVERSITY OF PENNSYLVANIA
K99CA252600	Role of Gstt1 in metastatic maintenance and self-renewal in PDA	CHRISTINA FERRER	MASSACHUSETTS GENERAL HOSPITAL

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K99CA255926	Mechanistic insights into lysosomal nutrient efflux in cancer	KACPER ROGALA	WHITEHEAD INSTITUTE FOR BIOMEDICAL RES
K99CA255928	Understanding the effects of dietary interventions on pancreatic ductal adenocarcinoma therapy cancer	EVAN CHEN LIEN	MASSACHUSETTS INSTITUTE OF TECHNOLOGY
K99CA255936	Mechanisms of translational output control in pancreatic cancer	SIMONE CHRISTINE HAUSMANN	UNIVERSITY OF TX MD ANDERSON CAN CTR
K99CA256525	Integrating epidemiologic, clinical, genomic and metabolomic profiles to predict pancreatic cancer risk in a multiethnic population	BRIAN HUANG	UNIVERSITY OF SOUTHERN CALIFORNIA
K99CA259224	Investigating the metabolic regulation of tumor desmoplasia	SIMON SCHWÖRER	SLOAN-KETTERING INST CAN RESEARCH
K99CA263005	Origin, diversification and function of pancreatic cancer associated fibroblasts	LU HAN	MEDICAL UNIVERSITY OF SOUTH CAROLINA
K99CA263154	Investigating Cellular Communication in the Tumor Microenvironment in Pancreatic Cancer	NINA G STEELE	UNIVERSITY OF MICHIGAN AT ANN ARBOR
K99CA266939	Elucidating determinants of metastasis suppression in pancreatic cancer	KALOYAN M. TSANOV	SLOAN-KETTERING INST CAN RESEARCH
K99CA267171	Integrating Spatial Omics and Drug Imaging to Dissect the Role of Pancreatic Tumor Microenvironment in Drug Resistance	GUOLAN LU	STANFORD UNIVERSITY
K99CA267176	Disrupting glutathione dependency in pancreatic cancer	ZERIBE CHIKE NWOSU	UNIVERSITY OF MICHIGAN AT ANN ARBOR
K99CA267561	Characterization of regulatory landscape of pancreatic cancer subtypes.	DEBORAH ANN WEIGHILL	UNIV OF NORTH CAROLINA CHAPEL HILL
K99CA276700	Mechanistic Basis for ERK in driving KRAS-dependent pancreatic cancer	JENNIFER E KLOMP	UNIV OF NORTH CAROLINA CHAPEL HILL
K99CA276804	Targeting Pancreatic Cancer Senescence with ImmunoPET	EDWIN CHARLES PRATT	SLOAN-KETTERING INST CAN RESEARCH
K99CA283277	Targeting Perp in PDAC tumor and cancer cachexia	ANEESHA DASGUPTA	INDIANA UNIVERSITY INDIANAPOLIS
K99CA283664	The crosstalk between obesity-induced fatty liver and liver metastasis	CHANGYU ZHU	SLOAN-KETTERING INST CAN RESEARCH
K99CA286709	Elucidating the role of hepatic ketogenesis in pancreatic cancer cachexia and recovery	PAIGE C ARNESON-WISSINK	OREGON HEALTH & SCIENCE UNIVERSITY
K99CA293142	Using Single-cell and Spatial Multi-omics to Improve Adoptive Cell Therapy against Pancreatic Cancer	YAPENG SU	FRED HUTCHINSON CANCER CENTER
K99EB033580	Machine Perception Nanosensor Array Platform to Capture Whole Disease Fingerprints of Early Stage Pancreatic Cancer	MIJIN KIM	SLOAN-KETTERING INST CAN RESEARCH
K99GM159354	Metabolic regulation of pancreatic metaplasia and neoplasia	MEGAN DEANNA RADYK	UNIVERSITY OF MICHIGAN AT ANN ARBOR

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P01CA084203	Photodynamic Priming of Cancer and Image-guidance for Optimal Immune Response	TAYYABA HASAN, EDWARD V MAYTIN, BRIAN W. POGUE, STEPHEN PEREIRA, GUILLERMO J TEARNEY, BRETT E BOUMA, KENNETH K WANG, BRYAN QUILTY SPRING, VINAY CHANDRASEKHARA	MASSACHUSETTS GENERAL HOSPITAL
P01CA117969	Genetics and Biology of Pancreatic Ductal Adenocarcinoma	RONALD ANTHONY DEPINHO, LEWIS C. CANTLEY, DOUGLAS HANAHAN, TYLER E. JACKS, MD WEISSLEDER, MARK REDSTON, SARAH P THAYER, JAMES A. DECAPRIO, GERALD C CHU, ANIRBAN MAITRA, CYRIL HENRI BENES, PHILLIP ANDREW FUTREAL, NABEEL EL-BARDEESY, RAGHU KALLURI, HUAMIN WANG, JAMES WESLEY HORNER	UNIVERSITY OF TX MD ANDERSON CAN CTR
P01CA203657	Defining RAS isoform- and mutation-specific roles in oncogenesis	CHANNING J. DER, LEE M GRAVES, SHARON L CAMPBELL, ADRIENNE D COX, CHRISTOPHER M COUNTER	UNIV OF NORTH CAROLINA CHAPEL HILL
P01CA217798	Pancreatic Cancer Metastasis	SURINDER K. BATRA, MICHAEL A. HOLLINGSWORTH, PANKAJ KUMAR SINGH, MANEESH JAIN, SARAH P THAYER	UNIVERSITY OF NEBRASKA MEDICAL CENTER
P01CA236585	Chemoprevention and mechanisms of obesity-promoted pancreatic adenocarcinoma	GUIDO ERWIN MICHAEL EIBL, JUAN ENRIQUE ROZENGURT, STEPHEN J. PANDOL, VAY LIANG W GO	UNIVERSITY OF CALIFORNIA LOS ANGELES
P01CA236778	The role of the macroenvironment in pancreatic cancer-induced cachexia	DENIS C GUTTRIDGE, TERESA A ZIMMERS, MICHAEL C. OSTROWSKI, LEONIDAS G. KONIARIS, MARTIN JOHN ROMEO, HONG LI	MEDICAL UNIVERSITY OF SOUTH CAROLINA

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P01CA244114	Pancreatic Cancer Development: Genetic and Immune Regulation	SEUNG K KIM, LAURA D ATTARDI, MARA H. SHERMAN, EDGAR G. ENGLEMAN, WALTER GWANG-UP PARK, GARRY P NOLAN, STEVEN E ARTANDI	STANFORD UNIVERSITY
P01CA265762	Overcoming mechanisms of therapeutic resistance in pancreatic ductal adenocarcinoma	TONY R. HUNTER, RONALD M EVANS, REUBEN SHAW, SUSAN M KAECH, HERVE TIRIAC, GEOFFREY MYLES WAHL	SALK INSTITUTE FOR BIOLOGICAL STUDIES
P20GM109024	Center for Diagnostic and Therapeutic Strategies in Pancreatic Cancer	SATHISH VENKATACHALEM, SANKU MALLIK, BIN GUO, GUODONG LIU, ERXI WU, KATIE REINDL, ESTELLE LECLERC, MOHIUDDIN QUADIR, JIHA KIM, YONGKI CHOI, RICK J JANSEN, JOHN CURLEE WILKINSON, MEGAN ORR, BUDDHADEV LAYEK, ROBERTO GOMES, SAIKAT BASU	NORTH DAKOTA STATE UNIVERSITY
P50CA196510	Washington University SPORE in Pancreatic Cancer	WILLIAM G HAWKINS, RYAN C FIELDS, GRAHAM A. COLDITZ, ALBERT CRAIG LOCKHART, WILLIAM E. GILLANDERS, DAVID G DENARDO, ANDREA WANG-GILLAM	WASHINGTON UNIVERSITY
P50CA221707	MD Anderson Cancer Center SPORE in Gastrointestinal Cancer	SCOTT KOPETZ, ANIRBAN MAITRA, DIPEN M. MARU, JEFFREY S MORRIS, PATRICK HWU, DAVID JOHN TWEARDY, GAURI VARADHACHARY, YING YUAN, MICHAEL J OVERMAN, SHUBHAM PANT	UNIVERSITY OF TX MD ANDERSON CAN CTR
P50CA257881	The Memorial Sloan Kettering Cancer Center SPORE in Pancreas Cancer	EILEEN MARY O'REILLY, CHRISTINE A IACOBUZIO-DONAHUE, ALICE CHIA- CHI WEI, VINOD P BALACHANDRAN, OLCA BASTURK,	SLOAN-KETTERING INST CAN RESEARCH

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		MARINELA CAPANU, JASON S. LEWIS	
P50CA257911	Selective Targeting of Pancreatic Cancer SPORE	JEN JEN YEH, CHANNING J. DER, GIANPIETRO DOTTI, ALINA IUGA, MICHAEL R KOSOROK, ALBERT SIDNEY BALDWIN, JONATHAN S. SERODY	UNIV OF NORTH CAROLINA CHAPEL HILL
P50CA272213	Washington University SPORE in Pancreatic Cancer	DAVID G DENARDO, RYAN C FIELDS, WILLIAM G HAWKINS, KIAN H LIM, GRAHAM A. COLDITZ, WILLIAM E. GILLANDERS	WASHINGTON UNIVERSITY
R00AR071508	The Extracellular Matrix in Muscle Atrophy	ERIN E TALBERT	UNIVERSITY OF IOWA
R00CA204725	Exploring Glycobiology and Discovering Biomarkers for Pancreatic Cancer	DANNIELLE ENGLE	SALK INSTITUTE FOR BIOLOGICAL STUDIES
R00CA218891	Targeting Malic Enzyme 3 as a Synthetic Lethality Target in Pancreatic Cancer	PRASENJIT DEY	ROSWELL PARK CANCER INSTITUTE CORP
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
R00CA229979	Experimental evolution of pancreatic cancer	ALVIN MAKOHON-MOORE	HACKENSACK UNIVERSITY MEDICAL CENTER
R00CA241110	Senescence-Associated Secretory Phenotype (SASP) modulation of the tumor microenvironment as a therapeutic strategy for KRAS-driven tumors	MARCUS A. RUSCETTI	UNIV OF MASSACHUSETTS MED SCH WORCESTER
R00CA241357	Disrupting macrophage metabolism to reduce immunosuppression and enhance therapy in pancreatic cancer	CHRISTOPHER J. HALBROOK	UNIVERSITY OF CALIFORNIA-IRVINE
R00CA245122	The role of Sin1 in Kras-driven cancer	PAU CASTEL	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R00CA248495	Interrogating the RAS interactome for therapeutic vulnerabilities	HEMA ADHIKARI	WASHINGTON UNIVERSITY
R00CA248838	Targeting aspartate biosynthesis in pancreatic tumors	JAVIER GARCIA BERMUDEZ	UT SOUTHWESTERN MEDICAL CENTER
R00CA252009	Function of mesothelial cells in the tumor microenvironment of pancreatic ductal adenocarcinoma	HUOCONG HUANG	UT SOUTHWESTERN MEDICAL CENTER
R00CA252153	Dissecting the oncogenic and pro-metastatic roles of PTHLH-mediated calcium signaling in pancreatic cancer	JASON R. PITARRESI	UNIV OF MASSACHUSETTS MED SCH WORCESTER

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R00CA252600	Role of Gstt1 in metastatic maintenance and self-renewal in PDA	CHRISTINA FERRER	UNIVERSITY OF MARYLAND BALTIMORE
R00CA255926	Mechanistic insights into lysosomal nutrient efflux in cancer	KACPER ROGALA	STANFORD UNIVERSITY
R00CA255928	Understanding the effects of dietary interventions on pancreatic ductal adenocarcinoma therapy cancer	EVAN CHEN LIEN	VAN ANDEL RESEARCH INSTITUTE
R00CA256525	Integrating epidemiologic, clinical, genomic and metabolomic profiles to predict pancreatic cancer risk in a multiethnic population	BRIAN HUANG	UNIVERSITY OF SOUTHERN CALIFORNIA
R00CA259224	Investigating the metabolic regulation of tumor desmoplasia	SIMON SCHWÖRER	UNIVERSITY OF CHICAGO
R00CA263154	Investigating Cellular Communication in the Tumor Microenvironment in Pancreatic Cancer	NINA G STEELE	HENRY FORD HEALTH SYSTEM
R00CA267171	Integrating Spatial Omics and Drug Imaging to Dissect the Role of Pancreatic Tumor Microenvironment in Drug Resistance	GUOLAN LU	STANFORD UNIVERSITY
R00CA267176	Disrupting glutathione dependency in pancreatic cancer	ZERIBE CHIKE NWOSU	CORNELL UNIVERSITY
R00EB033580	Machine Perception Nanosensor Array Platform to Capture Whole Disease Fingerprints of Early Stage Pancreatic Cancer	MIJIN KIM	GEORGIA INSTITUTE OF TECHNOLOGY
R01AR060209	FoxO signaling and skeletal muscle atrophy	ANDREW ROBERT JUDGE	UNIVERSITY OF FLORIDA
R01AR063786	Identification of key tumor cell-released factors that induce cachexia	YI-PING LI, SYED H JAFRI	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
R01AR072714	NF-kB Regulation of the Muscle Microenvironment in Cancer Cachexia	DENIS C GUTTRIDGE	MEDICAL UNIVERSITY OF SOUTH CAROLINA
R01AR081648	The Complement System and Cancer Cachexia	ANDREW ROBERT JUDGE, CARL ATKINSON	UNIVERSITY OF FLORIDA
R01CA075059	Dysregulation of TGF Beta Action Pancreatic Cancer	MURRAY KORC	UNIVERSITY OF CALIFORNIA-IRVINE
R01CA111754	Developing new therapeutic strategies for distinct Ras-driven cancers	KAREN M CICHOWSKI	BRIGHAM AND WOMEN'S HOSPITAL
R01CA112314	Mechanism and Anti-Cancer Activity of SCFA-Hexosamine Analogs	KEVIN J YAREMA, FREDERICK J KRAMBECK	JOHNS HOPKINS UNIVERSITY
R01CA124723	Role of HSP70 in Pancreatic Diseases	SUNDARAM RAMAKRISHNAN, ELI GILBOA, ASHOK K SALUJA	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
R01CA150190	Targeting Pancreatic Cancer Using Peptide Chemistry: From Bench to Bedside	DEBABRATA MUKHOPADHYAY, DALE F MIERKE, MARK R SPALLER	MAYO CLINIC JACKSONVILLE
R01CA154451	Ultrasound-enhanced drug penetration for treatment of pancreatic cancer	JOO HA HWANG	STANFORD UNIVERSITY

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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 M LOWY	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R01CA160417	Mitophagy in Tumor Microenvironment	DAOLIN TANG	UT SOUTHWESTERN MEDICAL CENTER
R01CA161976	Reprogramming the Tumor Microenvironment in Pancreas Cancer to Enhance Immunotherapy	NIPUN B. MERCHANT	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
R01CA163649	Targeting MUC1-Mediated Tumor-Stromal Metabolic Cross-Talk in Pancreatic Cancer	PANKAJ KUMAR SINGH	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA163764	On the path to the clinic: Lead optimization and pathway analysis of the pancreatic cancer-selective drug conjugate SW V-49	WILLIAM G HAWKINS, DIRK M. SPITZER	WASHINGTON UNIVERSITY
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 INDIANAPOLIS
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	LEI ZHENG	JOHNS HOPKINS UNIVERSITY
R01CA174294	Multifunctional immunoPET tracers for pancreatic and prostate cancer	ANNA M WU, ROBERT E REITER	BECKMAN RESEARCH INSTITUTE/CITY OF HOPE
R01CA174761	Role of acetyl-CoA in linking cancer cell metabolism and epigenetics	KATHRYN ELAINE WELLEN	UNIVERSITY OF PENNSYLVANIA
R01CA176647	Mutant p53 as actionable cancer-specific target	UTE MARTHA MOLL	STATE UNIVERSITY NEW YORK STONY BROOK
R01CA176828	Using Markers to Improve Pancreatic Cancer Screening	MICHAEL G. GOGGINS	JOHNS HOPKINS UNIVERSITY
R01CA177670	The Impact of Macrophage Origin on the Pathogenesis and Treatment Resistance of Pancreatic Cancer	DAVID G DENARDO	WASHINGTON UNIVERSITY
R01CA180949	Early detection of pancreatic cancer in diabetics	RU CHEN, SHENG PAN	BAYLOR COLLEGE OF MEDICINE
R01CA181445	Interrogating the response of the tumor microenvironment to combination immunotherapy using a microfluidic platform	ALBERT FOLCH, RAYMOND J MONNAT, ROBERT C ROSTOMILY	UNIVERSITY OF WASHINGTON
R01CA182311	High dose radiation therapy to direct immune responses to pancreatic cancer	MICHAEL JAMES GOUGH	PROVIDENCE PORTLAND MEDICAL CENTER
R01CA182495	Discovering Spatial Mechanisms Regulating Metastatic Invadopodia in PDAC	RICHARD L. KLEMKE	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R01CA183984	A novel miR-198 replacement therapy for pancreatic cancer	QIZHI C. YAO	BAYLOR COLLEGE OF MEDICINE

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R01CA186338	ZIP4 is a Novel Molecular Target in Human Pancreatic Cancer	MIN LI, MARTIN ERNESTO FERNANDEZ-ZAPICO	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA186662	Novel Small Molecule MDM2 Inhibitors for Pancreatic Cancer Therapy	RUIWEN ZHANG	UNIVERSITY OF HOUSTON
R01CA188134	Nrf2 Regulation of Ductal Pancreatic Cancer Etiology and Treatment Response	DAVID A TUVESON	COLD SPRING HARBOR LABORATORY
R01CA188654	MR-HIFU induced drug delivery for pancreatic cancer treatment	DONGHOON LEE	UNIVERSITY OF WASHINGTON
R01CA193887	TARGETING EXTRACELLULAR MATRIX-CANCER STEM CELL INTERACTIONS IN PANCREATIC CANCER	WILLIAM H MATSUI	UNIVERSITY OF TEXAS AT AUSTIN
R01CA194321	Imaging drug uptake and distribution in chemoradiation therapy of pancreatic cancer	JOHN L HUMM, NAGAVARAKISHORE PILLARSETTY, ABRAHAM WU, KENNETH H. YU, MAEVE AINE LOWERY	SLOAN-KETTERING INST CAN RESEARCH
R01CA194941	Suppression of pancreatic tumorigenesis by the PTF1 transcription factor network	LEWIS C MURTAUGH, RAYMOND J. MACDONALD	UNIVERSITY OF UTAH
R01CA195473	Repurposing Disulfiram: A Novel Strategy to Help Cancer Patients Regain Muscle	AMINAH JATOI, MARTIN ERNESTO FERNANDEZ-ZAPICO	MAYO CLINIC ROCHESTER
R01CA195651	Clinical Significance of Pancreatic Cancer Differentiation and Dedifferentiation	HUAMIN WANG, KEPING XIE	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA196639	Prevention of solar UV-induced skin cancer by targeting LTA4H	LIANG LIU, ZIGANG DONG	UNIVERSITY OF MINNESOTA
R01CA196941	Novel Signaling Pathways Regulating Pancreatic Cancer Pathogenesis	HUAMIN WANG	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA197296	Targeting the Immunosuppressive Tumor Microenvironment of Pancreatic Cancer with a Neoadjuvant Platform Clinical Trial	ELIZABETH M. JAFFEE, WILLIAM REECE BURNS, LEI ZHENG	JOHNS HOPKINS UNIVERSITY
R01CA197916	Targeting the liver for immunotherapy in pancreatic cancer	GREGORY L BEATTY	UNIVERSITY OF PENNSYLVANIA
R01CA197999	Development of Quinoxaline Based IKKbeta Inhibitors for Kras Driven Cancers	AMARNATH (AMAR) NATARAJAN	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R01CA198090	Integrated Signaling in Pancreatic Cancer Progression	ROBERT S BRESALIER, KEPING XIE	UNIVERSITY OF TX MD ANDERSON CAN CTR
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	ROBERT M STRAUBINGER, MARTIN CLYNES, WEN WEE MA, CHRIS SCOTT, NIALL BARRON	STATE UNIVERSITY OF NEW YORK AT BUFFALO
R01CA198128	Exploiting Caveolae-Dependent Albumin Endocytosis to optimize Therapy in Pancreatic Cancer	TERENCE MARQUES WILLIAMS	BECKMAN RESEARCH INSTITUTE/CITY OF HOPE

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R01CA199064	Tumor Subtypes and Therapy Response in Pancreatic Cancer	JEN JEN YEH, SUSAN TSAI, LEE M GRAVES, GARY L. JOHNSON	UNIV OF NORTH CAROLINA CHAPEL HILL
R01CA199646	Optimizing Ultrasound Enhanced Delivery of Therapeutics	FLEMMING FORSBERG	THOMAS JEFFERSON UNIVERSITY
R01CA200007	Multiplexed imaging of biliary intra-epithelial neoplasia	ERIC J SEIBEL, THOMAS D WANG	UNIVERSITY OF WASHINGTON
R01CA201318	The Paradoxical Role of mTORC1 in the Growth of Nutrient-deprived Pancreatic Cancer Cells Harboring Ras Mutations	CRAIG B THOMPSON	SLOAN-KETTERING INST CAN RESEARCH
R01CA203108	Prognostic Biomarkers for ZIP4-mediated Cachexia in Pancreatic Cancer	MIN LI, YI-PING LI	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA203890	COMBINED TUMOR AND STROMAL TARGETING TO IMPROVE PANCREATIC CANCER RESPONSE TO IMMUNOTHERAPY	DAVID G DENARDO	WASHINGTON UNIVERSITY
R01CA204228	Comprehensive genetic dissection of druggable KRAS targets	STEVEN D LEACH	DARTMOUTH COLLEGE
R01CA204232	Ferroptosis, Cellular Metabolism, and Cancer	XUEJUN JIANG	SLOAN-KETTERING INST CAN RESEARCH
R01CA204969	Uncovering Role of Exosomes in Regulating Pancreatic Cancer Cell Metabolism	DEEPAK NAGRATH	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA206069	Development of Targeted Nanotechnology Platform for Pancreatic Cancer	SUBHASH C. CHAUHAN	UNIVERSITY OF TEXAS RIO GRANDE VALLEY
R01CA206105	Regulation of Pancreatic Oncogenesis by the Gut Microbiome	DIANE M SIMEONE, DEEPAK SAXENA, GEORGE MILLER	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
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	UNIVERSITY OF TX MD ANDERSON CAN CTR
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 M PIWNICA-WORMS	UNIVERSITY OF TX MD ANDERSON CAN CTR
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
R01CA208253	Enhancing immune therapy in pancreatic cancer by targeting IL-6	GREGORY B. LESINSKI	EMORY UNIVERSITY

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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 AT ANN ARBOR
R01CA208401	Protein and proteolytic activity biomarkers of early stage pancreatic cancer	PAUL TEMPST, KENNETH H. YU	SLOAN-KETTERING INST CAN RESEARCH
R01CA208514	Mechanisms of durable antitumor immunity via CD26hiCD4+ T cells	CHRYSTAL MARY PAULOS	EMORY UNIVERSITY
R01CA208517	Determinants of pancreatic cancer and malignant melanoma phenotypes in CDKN2A hereditary kindreds	GLORIA M. PETERSEN, MARTIN ERNESTO FERNANDEZ-ZAPICO, HU LI	MAYO CLINIC ROCHESTER
R01CA209798	Investigating the cause of racial/ethnic disparity in pancreatic cancer incidence	VERONICA WENDY SETIAWAN	UNIVERSITY OF SOUTHERN CALIFORNIA
R01CA209886	Developing MRI-Guided Preventive Dendritic Cell Vaccination Strategy to Avoid Post-surgical Pancreatic Cancer Recurrence and Metastasis	ZHUOLI ZHANG, VAHID YAGHMAI	UNIVERSITY OF CALIFORNIA-IRVINE
R01CA210192	Targeted Nanotherapy for Pancreatic Cancer	SUBHASH C. CHAUHAN	UNIVERSITY OF TEXAS RIO GRANDE VALLEY
R01CA210439	Targeting the Metabolic Basis of Cachexia in Pancreatic Cancer	PANKAJ KUMAR SINGH	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA210553	Image-guided ultrasound therapy and drug delivery in pancreatic cancer	KATHERINE W 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
R01CA211070	The Pancreatic Cancer Microenvironment	RUI KANG	UT SOUTHWESTERN MEDICAL CENTER
R01CA211082	Optical imaging of pancreas cancer organoids for drug development and personalized treatment	MELISSA CAROLINE SKALA	MORGRIDGE INSTITUTE FOR RESEARCH, INC.
R01CA211087	Noninvasive prediction of tumor response to gemcitabine using MRI	GUANSHU LIU	HUGO W. MOSER RES INST KENNEDY KRIEGER
R01CA211098	Thrombin-dependent mechanisms of pancreatic ductal adenocarcinoma disease	MATTHEW J. FLICK, STEPHEN F KONIECZNY	UNIV OF NORTH CAROLINA CHAPEL HILL
R01CA211176	Preclinical Analyses of NAD Kinase as a Redox Vulnerability for the Treatment of Pancreatic Cancer	SARAH H. ELSEA	BAYLOR COLLEGE OF MEDICINE
R01CA211687	Role of nonsense mediated RNA decay in pancreatic cancer	MARK REID PHILIPS	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R01CA211878	Common Genetically Altered Pathways as Targets for Therapy in Pancreatic Cancer	AGNIESZKA WITKIEWICZ, ERIK KNUDSEN	ROSWELL PARK CANCER INSTITUTE CORP
R01CA212086	Optimizing the Treatment of Pancreatic Adenocarcinoma	CHIN HUR, CHUNG YIN KONG	COLUMBIA UNIVERSITY HEALTH SCIENCES

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R01CA212350	Stroma Targeted Theranostic Nanoparticles for Pancreatic Cancer	LACEY R MCNALLY	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA212600	Targeting HuR to improve a synthetic lethal therapy for pancreatic cancer	JONATHAN BRODY	OREGON HEALTH & SCIENCE UNIVERSITY
R01CA213214	Targeting the RNA Exosome for Cancer Therapeutics	MATS LJUNGMAN, NOURI NEAMATI, VAIBHAV SAHAI	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA213233	Exosomes in Cancer Therapy	RAGHU KALLURI	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA213278	Reprogramming Tumor Microenvironment by Nanoparticle	PRIYABRATA MUKHERJEE	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA214793	Elucidating and targeting subtype-specific driver in pancreatic cancer	HAOQIANG YING	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA215471	Dectin-1 signaling drives pancreatic oncogenesis by inducing macrophage-mediated adaptive immune suppression	KWOK KIN WONG, DAFNA BAR-SAGI, GEORGE MILLER	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R01CA215498	Functions of the LKB1 tumor suppressor in control in metabolism and epigenetics	NABEEL EL-BARDEESY	MASSACHUSETTS GENERAL HOSPITAL
R01CA215607	Targeting cysteine import to induce ferroptotic cell death in pancreatic cancer	KENNETH P. OLIVE	COLUMBIA UNIVERSITY HEALTH SCIENCES
R01CA216853	Metabolic Regulation of Tumor Progression, Metastasis and Chemoresistance by SIRT5/ELK3 signaling in Pancreatic Cancer	PANKAJ KUMAR SINGH	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA216879	Targeted Molecular Imaging of Plectin-1; Bench to bedside and back again	JULIE L SUTCLIFFE, KIMBERLY A. KELLY	UNIVERSITY OF CALIFORNIA AT DAVIS
R01CA216987	K-Ras sumoylation in cell proliferation and transformation	WEI DAI, YUAN CHEN	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R01CA217907	Galpha13 and pancreatic cancer progression	HIDAYATULLAH G. MUNSHI	NORTHWESTERN UNIVERSITY AT CHICAGO
R01CA217989	Exosomes as Endocrine Signaling Molecules in Cancer Cachexia	DANIEL L. MARKS	OREGON HEALTH & SCIENCE UNIVERSITY
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	Application of 4D proteomics and super-resolution microscopy in extracellular vesicle and particle-borne biomarker discovery for early pancreatic cancer detection	DAVID CHARLES LYDEN, JACOB GERI, HAIYING ZHANG	WEILL MEDICAL COLL OF CORNELL UNIV
R01CA219670	Targeting novel therapeutic vulnerabilities in LKB1 mutant tumors.	NABEEL EL-BARDEESY, KWOK KIN WONG	MASSACHUSETTS GENERAL HOSPITAL
R01CA220236	Wnt/?-catenin Signaling in Pancreatic Oncogenesis	ANIRBAN MAITRA	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA220237	UBAP2, A New Molecule in Pancreatic Cancer Progression	PRIYABRATA MUKHERJEE	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR

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R01CA220468	Bottlebrush polymer prodrugs for targeted delivery of combination therapies and *in vivo* imaging of pharmacological response	JEREMIAH ALLEN JOHNSON	MASSACHUSETTS INSTITUTE OF TECHNOLOGY
R01CA222049	Histopathologic validation of 89Zr-DFO-HuMab-5B1 PET/CT imaging in CA 19-9 positive pancreatic cancer	NEETA PANDIT TASKAR, MICHAEL I D'ANGELICA, JASON S. LEWIS, WOLFGANG WEBER	SLOAN-KETTERING INST CAN RESEARCH
R01CA222594	THE EVOLUTION OF PGD ADDICTION IN HUMAN PANCREATIC CANCER	OLIVER GENE MCDONALD	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
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
R01CA222969	Targeting Dectin-2 on Tumor-associated Macrophages for the Treatment of Cancer	EDGAR G. ENGLEMAN	STANFORD UNIVERSITY
R01CA223204	Role of Lipocalin 2 in Pancreatic Cancer	ZOBEIDA CRUZ-MONSERRATE	OHIO STATE UNIVERSITY
R01CA223495	A HTS Approach to Discover Guanine Nucleotide-Competitive Inhibitors of Oncogenic KRAS	KENT ROSSMAN	UNIV OF NORTH CAROLINA CHAPEL HILL
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 L. ALLBRITTON, DAVID S. LAWRENCE	UNIVERSITY OF WASHINGTON
R01CA225637	Mechanism of APE1 in DNA damage response	SHAN YAN	UNIVERSITY OF NORTH CAROLINA CHARLOTTE
R01CA225955	Exploring Collateral Lethality for Development of Cancer Therapeutics	RONALD ANTHONY DEPINHO	UNIVERSITY OF TX MD ANDERSON CAN CTR
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	XIAO-OU SHU, VERONICA WENDY SETIAWAN	VANDERBILT UNIVERSITY MEDICAL CENTER
R01CA227485	Integrated Informatic and Experimental Evaluations of Cancer Chronotherapy	RON C. ANAFI, JOHN B HOGENESCH	UNIVERSITY OF PENNSYLVANIA

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R01CA227517	Translating Intestinal Radioprotection by EGLN Inhibition to Improve Clinical Outcomes in Unresectable Pancreatic Cancer	ALBERT KOONG, CULLEN MITSUO TANIGUCHI	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA227737	BRAVE hydrogels for interrogating cell-matrix interactions in pancreatic desmoplasia	CHIEN-CHI LIN	INDIANA UNIVERSITY INDIANAPOLIS
R01CA227849	Redox Modification and Targeting of Mutant KRas in Cancer	KATE SUZANNE CARROLL	UNIVERSITY OF FLORIDA
R01CA228406	Targeting immune stroma interactions in pancreatic cancer	GREGORY B. 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	MASATO YAMAMOTO, JULIA DAVYDOVA	UNIVERSITY OF MINNESOTA
R01CA229560	Role of ICAM1 in development and progression of pancreatic cancer	PETER STORZ	MAYO CLINIC JACKSONVILLE
R01CA229580	Fatty acid signaling in the pancreatic tumor microenvironment	MARA H. SHERMAN	SLOAN-KETTERING INST CAN RESEARCH
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	ROBERT H VONDERHEIDE, BEN Z STANGER	UNIVERSITY OF PENNSYLVANIA
R01CA230277	Development of a New Strategy to Treat Locally Advanced Pancreatic Cancer	SCOTT ANDREW GERBER	UNIVERSITY OF ROCHESTER
R01CA230442	PRedictiOn Algorithms for the DeTECTion of Early Stage Pancreatic Cancer (PRO-TECT)	BECHIEN WU	KAISER FOUNDATION RESEARCH INSTITUTE
R01CA231052	Counteracting molecular mechanisms of obesity dependent PDAC progression	MICHAEL NATHAN VANSAUN	UNIVERSITY OF KANSAS MEDICAL CENTER
R01CA233944	Rapid and flexible precision oncology mouse models of epithelial malignancies epithelial malignancies	SCOTT W. LOWE	SLOAN-KETTERING INST CAN RESEARCH
R01CA235412	Mechanistic Understanding for the Role of Lin28b in Pancreatic Cancer Progression	RAUL MOSTOSLAVSKY, NABEEL EL-BARDEESY, DAVID TSAI TING	MASSACHUSETTS GENERAL HOSPITAL
R01CA235672	Novel CCR2 PET for Pancreatic Cancer Imaging and Prediction of Response to Standard and CCR2-Targeted Therapy	FARROKH DEHDASHTI, KIAN H LIM, YONGJIAN LIU	WASHINGTON UNIVERSITY
R01CA236118	Role of the METTL13 Lysine Methyltransferase in Signaling and Cancer	OR P. GOZANI, PAWEL K. MAZUR	STANFORD UNIVERSITY
R01CA236389	STAT3 is a Critical Regulator of Tumor Cell Plasticity	NANCY C. REICH MARSHALL	STATE UNIVERSITY NEW YORK STONY BROOK
R01CA236949	Role of SETD5 in Chromatin Regulation and Tumorigenesis	PAWEL K. MAZUR, OR P. GOZANI	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA236965	Targeting PYK2 for the treatment of PDAC	JING HU	UNIVERSITY OF PITTSBURGH AT PITTSBURGH

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R01CA237037	Developing translationally-relevant genetically engineered mouse models of lung adenocarcinoma for investigations in cancer immunology	NIKHIL JOSHI	YALE UNIVERSITY
R01CA237250	3D carbon-nanotubes integrated microdevice for extracellular vesicle isolation and *in situ* sample preparation towards noninvasive pancreatic cancer diagnosis	SIYANG ZHENG	CARNEGIE-MELLON UNIVERSITY
R01CA237404	Lineage specifiers governing pancreatic cancer growth and molecular subtype	ERIC LEE SNYDER	UNIVERSITY OF UTAH
R01CA237569	Intravascular Delivery of Nanoclusters for Treatment of Deep-Seated Cancers with Magnetic Hyperthermia	OLEH TARATULA	OREGON STATE UNIVERSITY
R01CA237672	Adoptive T Cell Therapy for Pancreatic Cancer	CASSIAN YEE	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA239219	Imaging Acidosis and Immune Therapy in PDAC	SHARI PILON-THOMAS, ARIG A IBRAHIM HASHIM, ROBERT J. GILLIES	H. LEE MOFFITT CANCER CTR & RES INST
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 A MORGAN	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA240603	Identifying Molecular Drivers of Cellular Plasticity in Pancreatic Cancer	RUSHIKA MIRIAM PERERA	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA240654	NRF2-dependent redox signaling in pancreatic cancer	CHRISTINE IOK IN CHIO	COLUMBIA UNIVERSITY HEALTH SCIENCES
R01CA240814	Type I Interferon Pathway in Pancreatic Adenocarcinoma	SERGE Y FUCHS	UNIVERSITY OF PENNSYLVANIA
R01CA240818	Targeting NADPH Oxidase for Pancreatic Cancer Prevention and Therapy	WEIQIN LU	UNIVERSITY OF TEXAS EL PASO
R01CA241728	Bacterial biosensors for the prevention of gastrointestinal cancers	JEFF M HASTY, ROB KNIGHT	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R01CA241764	Combating Resistance of Pancreatic Cancer with a First-in-Class Dual Targeted PI3K/EGFR Inhibitor	JUDITH S LEOPOLD, ALNAWAZ REHEMTULLA	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA242003	Use of BCL-xL Proteolysis targeting chimeras to treat pancreatic cancer	GUANGRONG ZHENG, JOSE G. TREVINO, DAOHONG ZHOU	UNIVERSITY OF FLORIDA
R01CA243577	Targeted inhibition in stromal TGFβ activity in pancreatic cancer	ROLF A BREKKEN	UT SOUTHWESTERN MEDICAL CENTER
R01CA244142	Rewiring the myeloid cell response to adjuvants to improve tumor control	MICHAEL JAMES GOUGH	PROVIDENCE PORTLAND MEDICAL CENTER
R01CA244931	Targeting metabolic stress to induce pancreatic tumor cell death	COSTAS ANDREAS LYSSIOTIS	UNIVERSITY OF MICHIGAN AT ANN ARBOR

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R01CA244938	Exploiting Integrin Signaling to Overcome Resistance to Immunotherapy	DAVID G DENARDO, VINEET GUPTA	WASHINGTON UNIVERSITY
R01CA245005	POLQ Synthetic Lethality in HR-Deficient Pancreatic Adenocarcinoma	DIANE M SIMEONE, AGNEL SFEIR	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R01CA245081	Inhibitors of Oxidative Protein Folding For The Treatment of Cancer	NATHAN G. DOLLOFF	MEDICAL UNIVERSITY OF SOUTH CAROLINA
R01CA245323	Mechanisms and therapeutic targets of cancer metastasis	GREGORY L BEATTY	UNIVERSITY OF PENNSYLVANIA
R01CA247234	Role of Zinc Dependent EMT-Transcription Factors (EMT-TF) in Pancreatic Cancer Metastasis	MIN LI	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA247441	Vascularized tumor explants for drug testing	LANCE L. MUNN, DAN GABRIEL DUDA	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 C. CRAWFORD	HENRY FORD HEALTH SYSTEM
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	WILLIAM C ZAMBONI, SHA X CHANG, STEVEN K. LIBUTTI	UNIV OF NORTH CAROLINA CHAPEL HILL
R01CA247666	Use of a Nano-Enabled Platform for Pancreatic Cancer Immunotherapy	ANDRE ELIAS NEL, JEFFREY I ZINK	UNIVERSITY OF CALIFORNIA LOS ANGELES
R01CA247763	Targeting tumor and its microenvironment using nanotherapeutics for pancreatic cancer	SATYANARAYANA RACHAGANI	UNIVERSITY OF MISSOURI-COLUMBIA
R01CA247898	Targeting Epigenomic Regulators at the Replication Fork in PDAC	GWEN LOMBERK	MEDICAL COLLEGE OF WISCONSIN
R01CA247960	Machine learning accelerated on-line adaptive replanning	ERIC S PAULSON, X. ALLEN LI	MEDICAL COLLEGE OF WISCONSIN
R01CA248160	Stromal metabolism promotes therapeutic resistance in pancreatic cancer	COSTAS ANDREAS LYSSIOTIS	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA248277	Advancing Precision Oncology in a Humanized, Fully Autologous Mouse Model	RYAN C FIELDS, RICHARD A FLAVELL	WASHINGTON UNIVERSITY
R01CA248315	Branched chain amino acids and pancreatic cancer	KATHRYN ELAINE WELLEN, ZOLTAN P ARANY	UNIVERSITY OF PENNSYLVANIA
R01CA248323	New protein engineering-based tools and technologies for characterizing cell surface proteolysis in cancer cells for novel neo-epitope biomarkers and drug targets	JAMES A WELLS	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA248917	Targeting Focal Adhesion Kinase to Improve RT-inducted Tumor Immunity	DAVID G DENARDO, HYUN KIM, JULIE KRISTINA SCHWARZ	WASHINGTON UNIVERSITY

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R01CA249002	Fibroblast Heterogeneity in Pancreatic Cancer	DAVID A TUVESON	COLD SPRING HARBOR LABORATORY
R01CA249393	Mechanisms of immunotherapy response and resistance in pancreatic ductal adenocarcinoma	INGUNN MARGARETE STROMNES	UNIVERSITY OF MINNESOTA
R01CA250173	Endoplasmic Reticulum-to-Mitochondria Calcium Transfer in Pancreatic Cancer Development, Metastasis, and Treatment	JAMES KEVIN FOSKETT	UNIVERSITY OF PENNSYLVANIA
R01CA250469	Therapeutic Targeting Mitochondrial C1 Metabolism	LARRY H MATHERLY, CHARLES E. DANN, ALEEM GANGJEE	WAYNE STATE UNIVERSITY
R01CA250529	Leveraging Vulnerabilities Induced by STING Activation in Pancreatic Cancer	TIMOTHY R DONAHUE, CAIUS GABRIEL RADU	UNIVERSITY OF CALIFORNIA LOS ANGELES
R01CA250557	Imaging Modulation of Immune Phenotype	KATHERINE W FERRARA, RONALD LEVY	STANFORD UNIVERSITY
R01CA250917	Origins and functions of pancreatic cancer-associated fibroblasts	MARA H. SHERMAN	SLOAN-KETTERING INST CAN RESEARCH
R01CA251405	Targeting Transglutaminase 2 in cancer cachexia	AZEDDINE ATFI	VIRGINIA COMMONWEALTH UNIVERSITY
R01CA251726	Targeting the autophagy-lysosome system to block pancreatic cancer	RUSHIKA MIRIAM PERERA	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA251816	Breaking down tumor immune privilege through targeted hypoxia reduction	MICHAEL A. CURRAN	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA252223	Mechanisms of Epigenetic Plasticity in PDAC	CHUNLING YI, ALESSANDRO GARDINI	GEORGETOWN UNIVERSITY
R01CA252225	Defining metabolic adaptations within the PDAC "arid" tumor microenvironment	CHI V. DANG, BEN Z STANGER	JOHNS HOPKINS UNIVERSITY
R01CA253316	HIFU-immunotherapy in pancreatic cancer	KATHERINE W FERRARA	STANFORD UNIVERSITY
R01CA254036	Urine and serum biomarkers for early diagnosis and risk assessment of pancreatic cancer	ANNA E. LOKSHIN, SURINDER K. BATRA, RANDALL BRAND	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
R01CA254110	Investigation of novel signaling protein in 3D and *in vivo* PDAC models using second generation Ref-1 inhibitors	MELISSA L. FISHEL, BUMSOO HAN	INDIANA UNIVERSITY INDIANAPOLIS
R01CA254268	Combining Irreversible Electroporation with Immunotherapy for the Systemic Treatment of Pancreatic Cancer	REBEKAH WHITE	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R01CA254806	Regulation and Function of Stromal Macropinocytosis in Pancreatic Ductal Adenocarcinoma	COSIMO COMMISSO	SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE
R01CA255039	Enhancing engineered T cell therapeutic efficacy for the treatment of pancreatic ductal adenocarcinoma	INGUNN MARGARETE STROMNES	UNIVERSITY OF MINNESOTA
R01CA255068	PRSS1 Mutation and Pancreatic Cancer Tumorigenesis	BAOAN JI	MAYO CLINIC JACKSONVILLE

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R01CA255074	Transcriptomic mechanisms underlying the immune modulating function and therapeutic efficacy of PARP inhibitors	TIMOTHY ANTHONY YAP	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA255661	Real-time MRI-guided adaptive radiotherapy of unresectable pancreatic cancer	RICARDO OTAZO	SLOAN-KETTERING INST CAN RESEARCH
R01CA255670	Mechanistic investigations of microbiome-driven aryl hydrocarbon receptor activity and macrophage function in pancreatic cancer.	TRACY L MCGAHA	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	SALLY A. AMUNDSON	COLUMBIA UNIVERSITY HEALTH SCIENCES
R01CA256911	Mitochondrial calcium signaling in pancreatic cancer metastasis and progression	SHENGYU YANG, PANKAJ KUMAR SINGH	PENNSYLVANIA STATE UNIV HERSHEY MED CTR
R01CA256969	Optimizing Pancreatic Cancer Management with Next Generation Imaging and Liquid Biopsy	ERIC COLLISSON, AJIT HARISHKUMAR GOENKA, ZHEN JANE WANG	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA256973	Molecular Imaging Probe(s) for Optical Surgical Navigation of Pancreatic Cancer	MICHAEL BOUVET, SURINDER K. BATRA	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R01CA257452	PQ6: Lipocalin-2 as a therapeutic target for prevention of cancer cachexia	TERESA A ZIMMERS, DANIEL L. MARKS	OREGON HEALTH & SCIENCE UNIVERSITY
R01CA257509	Relative Immunological Effectiveness (RIE) of Carbon Ion Radiation Therapy for Pancreatic Cancer	CHANDAN GUHA, XIAODONG WU	ALBERT EINSTEIN COLLEGE OF MEDICINE
R01CA258240	Universal Internal Standard for Reproducible Accurate Quantification of Exosome Protein Markers	DAVID M. LUBMAN, TUJIN SHI	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA258324	Engaging immunosuppressive myeloid cells in the TME for the treatment of pancreatic cancer	JEFFREY VICTOR RAVETCH, MIKAEL KARLSSON	ROCKEFELLER UNIVERSITY
R01CA258372	Role of extracellular matrix proteins and tumor stroma in DNA repair and cancer progression	TARU ELIISA MURANEN	BETH ISRAEL DEACONESS MEDICAL CENTER
R01CA258540	Development of irreversible electroporation-based rational combinations to potentiate the activity of cancer immunotherapy against pancreatic ductal adenocarcinoma	CHUN LI, Y. ALAN WANG	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA258712	Targeting MTOR signaling in pancreatic cancer	BRIAN C LEWIS	UNIV OF MASSACHUSETTS MED SCH WORCESTER
R01CA258917	Mitochondrial heterogeneity as the origin of chemoresistance in pancreatic cancer	ANDREA VIALE	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA259080	Preclinical development of a novel antibody conjugate for intraoperative detection of pancreatic cancer	AARON M. MOHS	UNIVERSITY OF NEBRASKA MEDICAL CENTER

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R01CA260249	Dissecting new mechanisms of lysosome quality control in health and disease	RUSHIKA MIRIAM PERERA	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA260340	Addressing Chemoresistance in Pancreatic and Ovarian Cancers: Photodynamic Priming and Repurposing of Tetracyclines using Targeted Photo-Activable Multi-Inhibitor Liposome	HUANG CHIAO HUANG	UNIV OF MARYLAND, COLLEGE PARK
R01CA260449	Exploiting gold nanoparticle as a probe to identify therapeutic targets	PRIYABRATA MUKHERJEE, RESHAM BHATTACHARYA	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA260678	Targeting KRAS and adenosine mediated immunosuppression in pancreatic cancer	CAIUS GABRIEL RADU, TIMOTHY R DONAHUE, ZEV A WAINBERG	UNIVERSITY OF CALIFORNIA LOS ANGELES
R01CA260752	Targeting the fibroblast-immune cell crosstalk to relieve immune suppression in the pancreatic cancer microenvironment	MARINA PASCA DI MAGLIANO	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA260860	Understanding Efficacy and Fe(II)-Promoted Activation of 1,2,4-Trioxolanes in Cancer	ERIC COLLISSON, ADAM R RENSLO	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA260955	Predicting Pancreatic Ductal Adenocarcinoma (PDAC) Through Artificial Intelligence Analysis of Pre-Diagnostic CT Images	DEBIAO LI, STEPHEN J. PANDOL, TEMEL TIRKES	CEDARS-SINAI MEDICAL CENTER
R01CA261251	Stroma penetrating and immune modulating nanoparticles for image-guided therapy of pancreatic cancer	LILY YANG, HUI MAO	EMORY UNIVERSITY
R01CA262414	Harnessing TNFa Signaling To Improve Therapeutic Response In Pancreatic Cancer	KIAN H LIM	WASHINGTON UNIVERSITY
R01CA262420	SLC6A14 as a unique drug target to treat pancreatic cancer	YANGZOM DOMA BHUTIA	TEXAS TECH UNIVERSITY HEALTH SCIS CENTER
R01CA262506	Re-wiring PDAC Tumor Immunity Through Dendritic Cells	DAVID G DENARDO, CARL DESELM	WASHINGTON UNIVERSITY
R01CA262516	Group 2 Innate Lymphoid Cell Regulation of Pancreatic Cancer Immunity	VINOD P BALACHANDRAN, TAHA MERGHOUB	SLOAN-KETTERING INST CAN RESEARCH
R01CA262526	Impact of CREB-driven mechanism in shaping the tumor-immune landscape	NAGARAJ S. NAGATHIHALLI	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
R01CA262580	Repolarizing the Tumor and Metastatic Microenvironments to Treat Patients with Pancreatic Cancer	SCOTT ANDREW GERBER, DAVID C LINEHAN	UNIVERSITY OF ROCHESTER
R01CA262822	Role of type 2 immune response in pancreatic cancer tumorigenesis	PRASENJIT DEY	ROSWELL PARK CANCER INSTITUTE CORP
R01CA263897	Stimuli-responsive mucin1-specific nanoparticles for efficacious combinatorial chemotherapy of pancreatic ductal adenocarcinoma	JUAN LUIS VIVERO-ESCOTO	UNIVERSITY OF NORTH CAROLINA CHARLOTTE
R01CA264133	PQ6: Therapeutic approaches for autonomic and neuroendocrine dysfunction in cancer cachexia	AARON GROSSBERG, DANIEL L. MARKS	OREGON HEALTH & SCIENCE UNIVERSITY

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R01CA264471	A Fragment-Based Strategy for K-RAS Covalent Inhibitors	SAMY MEROUEH	INDIANA UNIVERSITY INDIANAPOLIS
R01CA264843	Establishment and regulation of the immune suppressive microenvironment in pancreatic cancer	MARINA PASCA DI MAGLIANO	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA265050	New Therapuetics for Pancreatic Cancer	MARTIN ERNESTO FERNANDEZ-ZAPICO, MICHAEL T BARRETT	MAYO CLINIC ROCHESTER
R01CA265997	Co-targeting BET Bromodomain Proteins and MNK Kinases in Pancreatic Cancer	HIDAYATULLAH G. MUNSHI	NORTHWESTERN UNIVERSITY AT CHICAGO
R01CA266187	DIRAS3 disrupts K-RAS clustering and signaling, enhancing autophagy and response to autophagy inhibition	ROBERT C BAST, ZHEN LU	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA266472	Microbial- based targeting of major extracellular matrix components for improved therapy of pancreatic cancer	EDWIN MANUEL	BECKMAN RESEARCH INSTITUTE/CITY OF HOPE
R01CA266558	Targeting cell regulatory states to complement MEK/autophagy inhibition in pancreatic cancer	KENNETH P. OLIVE, GULAM ABBAS MANJI	COLUMBIA UNIVERSITY HEALTH SCIENCES
R01CA266759	Nanomedicine of Hedgehog and AKT/ERK Dual Inhibitors for Pancreatic Cancer	RAM I. MAHATO	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R01CA266828	Discovery of Glutaryl-CoA Dehydrogenase inhibitors for melanoma and pancreatic cancer	EDUARD A. SERGIENKO	SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE
R01CA267870	Studying the role of eIF4A in Pancreatic Cancer	CHRISTINE IOK IN CHIO	COLUMBIA UNIVERSITY HEALTH SCIENCES
R01CA268426	Mechanisms of myeloid cell driven pancreatic plasticity and carcinogenesis	MARINA PASCA DI MAGLIANO, TIMOTHY LOUIS FRANKEL	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA269025	Role of Hypoxia in Shaping the Tumor Stroma in Pancreatic Cancer	KYOUNG EUN LEE	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA269233	TGX-1214 - Combination Strategy for the Treatment of Advanced Pancreatic Cancer	GERARDO GUILLERMO MACKENZIE, MANSOOR M. AMIJI, JAMES E EGAN, EDWARD J KIM	UNIVERSITY OF CALIFORNIA AT DAVIS
R01CA269295	Lipid storage and catabolism as drivers of metastatic invasion	GINA LYNN RAZIDLO	MAYO CLINIC ROCHESTER
R01CA269565	The Role of HIF2 in Pancreatic Ductal Adenocarcinoma	ALBERT KOONG, CULLEN MITSUO TANIGUCHI	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA269651	Defining pro-metastatic drivers in the pancreatic cancer tumor microenvironment	MICHAEL PAUL KIM	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA269660	Pancreatic cancer-associated fibroblasts: function, detection, and regulation	EDNA CUKIERMAN	RESEARCH INST OF FOX CHASE CAN CTR
R01CA269811	Deploying Histotripsy Based Tumor Ablation Strategies to Treat Pancreatic Cancer	IRVING C ALLEN	VIRGINIA POLYTECHNIC INST AND ST UNIV

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R01CA269897	Potentiating a systemic antitumor response by interstitial localized ablative immunotherapy to synergize with immune checkpoint therapy for metastatic pancreatic tumors	WEI R. CHEN, MIN LI	UNIVERSITY OF OKLAHOMA
R01CA270025	Matricellular proteins of the CNN family as regulators of tumor-induced cachexia	SARAH M JUDGE	UNIVERSITY OF FLORIDA
R01CA270110	Role of Altered Nutrient Metabolism in Pancreatic Cancer	NADA Y. KALAANY	BOSTON CHILDREN'S HOSPITAL
R01CA270234	Molecular Basis of ME2-mediated Tumor Suppression in Pancreatic Cancer	PANKAJ KUMAR SINGH	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA270240	Proteostasis Reprogramming in Mutant KRAS-Driven Cancers	XI CHEN	BAYLOR COLLEGE OF MEDICINE
R01CA270251	A SYNTHETIC BIOMARKER TO UNIVERSALLY ASSESS THE RELATIVE CONTRIBUTION OF HEATHY AND CANCEROUS TISSUE TO CIRCULATING EV POOL	EMANUELE COCUCCI	OHIO STATE UNIVERSITY
R01CA270623	Combination Therapy for Pancreatic Cancer	SONG LI	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
R01CA271369	Targeting Stromal Influences on BCKA Addiction in PDAC Tumors	DEEPAK NAGRATH, THEODORE S LAWRENCE, SUNITHA NAGRATH	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA271510	Dissecting the role of Notch signaling in the pancreatic cancer microenvironment.	MARINA PASCA DI MAGLIANO, FILIP BEDNAR	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA271592	Normalizing PDAC stroma with PCBP2 siRNA nanoparticles to improve the antitumor activity of chemotherapy and immunotherapy	KUN CHENG	UNIVERSITY OF MISSOURI KANSAS CITY
R01CA272433	Macropinocytosis Inhibition as a Glutamine Mimetic Sensitization Strategy in Pancreatic Cancer	COSIMO COMMISSO	SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE
R01CA272628	Quantitative *In Vivo* 68Ga-Fibroblast-Activation-Protein-Inhibitors (FAPI)-46 PET Imaging of Cancer-Associated Fibroblasts (CAFs) in Pancreatic Ductal Adenocarcinoma (PDA)	AJIT HARISHKUMAR GOENKA	MAYO CLINIC ROCHESTER
R01CA272641	Preclinical Development of First-in-Class NDUFS7 Antagonists for the Treatment of Pancreatic Cancer	NOURI NEAMATI	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA272668	Multifactor risk scores with susceptibility gene mutations to enhance risk assessment of pancreatic cancer	ANN LAURA OBERG	MAYO CLINIC ROCHESTER
R01CA272732	Development of Microbial-Based Therapies to Suppress Macropinocytosis in Kras-Driven Cancers	EDWIN MANUEL	BECKMAN RESEARCH INSTITUTE/CITY OF HOPE

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R01CA272789	High Throughput Screening for SCAP Inhibitors as Pancreas Cancer Therapeutics	PETER J. ESPENSHADE	JOHNS HOPKINS UNIVERSITY
R01CA272876	Epigenetic regulation of pancreatic cancer subtype identity and tumorigenesis by PHF2	ANDREW LISS	MASSACHUSETTS GENERAL HOSPITAL
R01CA273023	Characterizing the role of MSRA in pancreatic tumorigenesis	CHRISTINE IOK IN CHIO	COLUMBIA UNIVERSITY HEALTH SCIENCES
R01CA273035	Highly Sensitive Detection of Occult Pancreatic Cancer Using Intraoperative Molecular Imaging	GEORGE POULTSIDES	STANFORD UNIVERSITY
R01CA273349	Truncated O-glycan-dependent mechanisms inducing metastatic dissemination in pancreatic cancer	MOORTHY P. PONNUSAMY, SURINDER K. BATRA	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R01CA274355	Understanding and targeting mutant splicing factors in pancreatic cancer	LUISA ESCOBAR HOYOS	YALE UNIVERSITY
R01CA274415	*In situ* cancer cell specific biomineralization to overcome nanoparticle delivery barriers and sensitize pancreatic cancer to radiotherapy	KONSTANTIN V SOKOLOV, SANG HYUN CHO, SUNIL KRISHNAN	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA274439	Optimization of High Frequency Irreversible Electroporation (H-FIRE) for tumor ablation and immune system activation in pancreatic cancer applications	IRVING C ALLEN	VIRGINIA POLYTECHNIC INST AND ST UNIV
R01CA275036	Tumor-intrinsic and paracrine roles of endoglin in pancreatic cancer	NAM Y LEE	UNIVERSITY OF ARIZONA
R01CA275081	Impact of RB activation on the pancreatic cancer epigenome and tumor microenvironment	AGNIESZKA WITKIEWICZ, ERIK KNUDSEN	ROSWELL PARK CANCER INSTITUTE CORP
R01CA275182	Investigating GLI transcription factors as regulators of the pancreatic cancer microenvironment	BENJAMIN ALLEN, MARINA PASCA DI MAGLIANO	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA275761	Develop Conditionally Armored CAR Macrophage Therapy for Pancreatic Cancer	PINGPING HOU	RUTGERS BIOMEDICAL AND HEALTH SCIENCES
R01CA276108	Dietary fatty acids drive pancreatic cancer development	MANDAR DEEPAK MUZUMDAR	YALE UNIVERSITY
R01CA276179	Advancing Systematic Delivery of Oncolytic Adenovirus for Pancreatic Cancer	JULIA DAVYDOVA	UNIVERSITY OF MINNESOTA
R01CA276193	Discovery of Novel Inhibitors Targeting trans-Golgi Network Acidification in Pancreatic Cancer	COSIMO COMMISSO, SUSANNE HEYNEN-GENEL	SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE
R01CA276268	Mechanisms of response and resistance to KRAS inhibition in pancreatic cancer	ANDREW JAMES AGUIRRE	DANA-FARBER CANCER INST
R01CA276347	Dissecting roles of Lunatic Fringe-dependent Notch signaling in pancreatic cancer	KELI XU	UNIVERSITY OF MISSISSIPPI MED CTR

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R01CA276378	Preclinical development of the novel inhibitor of apoptosis proteins S2/IAPinh for cancer therapy	DIRK M. SPITZER, WILLIAM G HAWKINS	WASHINGTON UNIVERSITY
R01CA276461	Targeting nutrient microenvironment imprinted therapy resistance in pancreatic cancer	ALEXANDER MUIR	UNIVERSITY OF CHICAGO
R01CA276480	Advanced Oncolytic Adenovirus Enabling Systemic Therapy of PDAC	MASATO YAMAMOTO	UNIVERSITY OF MINNESOTA
R01CA276512	Stromal and vascular inputs into pancreatic cancer tumor neighborhoods	BEN Z STANGER, M. CELESTE SIMON	UNIVERSITY OF PENNSYLVANIA
R01CA276732	Engineering Exosome for Pancreatic Cancer Targeting Therapies	SHI-HE LIU	UNIVERSITY OF TOLEDO HEALTH SCI CAMPUS
R01CA277161	A single-arm phase 2 study to evaluate the safety and efficacy of combination systematic chemotherapy and multiple rounds of endoscopic ultrasound-guided radiofrequency ablation in pancreatic cancer	NIRAV THOSANI, JENNIFER BAILEY LUNDBERG	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
R01CA277680	The CCK-B receptor signaling pathway as a driver of pancreatic cellular plasticity and carcinogenesis	JILL P SMITH, MARIAELENA PIEROBON	GEORGETOWN UNIVERSITY
R01CA278941	Understanding Pancreatic Cancer Immune Microenvironment and Treatment Response through Integrating *in vivo* Imaging with Immunophenotyping	JUN YAN, HAIXUN GUO	UNIVERSITY OF LOUISVILLE
R01CA279173	A novel, glutathione-dependent metabolic pathway drives metastatic outgrowth in pancreatic cancer	RAUL MOSTOSLAVSKY	MASSACHUSETTS GENERAL HOSPITAL
R01CA279487	Development of a precision medicine platform for circadian based therapeutics in pancreatic cancer	FARAZ BISHEHSARI	RUSH UNIVERSITY MEDICAL CENTER
R01CA279707	Contributions of the Adipose Tissue to the Development of Pancreatic Cancer	ZOBEIDA CRUZ-MONSERRATE	OHIO STATE UNIVERSITY
R01CA279713	RBFOX2 deregulation promotes pancreatic cancer progression through alternative splicing	KAREN M MANN	H. LEE MOFFITT CANCER CTR & RES INST
R01CA280071	Translating Hyperpolarized 13C MRI as a Novel Tool to Predict Treatment Response in Pancreatic Cancer	JEREMY WILLIAM GORDON, ZHEN JANE WANG	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA281098	Development of contrast agents to facilitate image-guided surgery	LACEY R MCNALLY, AJAY JAIN	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01CA281198	Collagen Signaling in Pancreatic Cancer	HOWARD C. CRAWFORD, JEAN-PHILIPPE FRANCOIS MARIE COPPE, RAFAEL A. FRIDMAN	HENRY FORD HEALTH + MICHIGAN STATE UNIVERSITY HEALTH SCIENCES
R01CA281207	Targeting cancer cachexia drivers using antibody-based approaches	AZEDDINE ATFI	VIRGINIA COMMONWEALTH UNIVERSITY

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R01CA282439	Irreversible Electroporation (IRE) Combined with CD40 Agonism as *In Situ* Vaccine Therapy for Pancreatic Cancer	REBEKAH WHITE, STEPHEN PHILIP SCHOENBERGER	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R01CA282478	Metabolic flux analysis and PDX models to understand therapeutic vulnerabilities following inhibition of Ref-1 redox signaling in pancreatic cancer	MARK R. KELLEY, MELISSA L. FISHEL	INDIANA UNIVERSITY INDIANAPOLIS
R01CA282786	Interrogating the Spatial and Functional Relevance of Microbes in Pancreatic Cancer and Metastasis	FLORENCIA MCALLISTER	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA283378	Mechanisms of p53 Engagement and Action at the Benign-to-Malignant Transition in Sporadic Tumorigenesis	SCOTT W. LOWE, DANA PE'ER	SLOAN-KETTERING INST CAN RESEARCH
R01CA283394	Stromal targeting to improve the efficacy of systemically administered drugs for pancreatic ductal adenocarcinomas	LUIS SOLORIO	PURDUE UNIVERSITY
R01CA283736	Innovative mRNA vaccines to enhance the efficacy of T-cell transfer therapies against solid tumors	CAIUS GABRIEL RADU, NORBERT PARDI	UNIVERSITY OF CALIFORNIA LOS ANGELES
R01CA283740	Utilizing nucleic acid scavengers to elucidate how DNA/RNA-containing DAMPs promote pancreatic cancer metastasis and to mitigate such processes	BRUCE ALAN SULLENGER, REBEKAH WHITE	DUKE UNIVERSITY
R01CA283925	Elucidating the mechanism of Ga13 mediated tumor suppression in pancreatic cancer	MARIO SHIELDS	NORTHWESTERN UNIVERSITY AT CHICAGO
R01CA285203	Exploring the role and potential of anti-viral drugs to sensitize cancer cells to chemotherapy	QING YI	METHODIST HOSPITAL RESEARCH INSTITUTE
R01CA285585	Peripheral Nerve Regulation of Pancreas Cancer Progression	JAMI LYNN SALOMAN	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
R01CA285774	Elucidation of hypoxia-induced metastatic reprogramming through the regulation of KDM8 function in pancreatic cancer	SHIN-HENG CHIOU	RUTGERS BIOMEDICAL AND HEALTH SCIENCES
R01CA285997	Collagen fibers and fragments regulate pancreatic cancer metabolism and growth.	MICHAEL KARIN, DAVID A. BRENNER	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R01CA286017	ROLES AND MECHANISMS OF TERTIARY LYMPHOID STRUCTURES IN ANTI-TUMOR IMMUNITY	ANDREW GUNDERSON	OHIO STATE UNIVERSITY
R01CA286615	Stomal Senescence Regulator of Tumor Immunity and Progression	DAVID G DENARDO, PAOLO PROVENZANO	WASHINGTON UNIVERSITY
R01CA287672	Optimizing anti-wild-type IDH1 therapy in pancreatic cancer	JORDAN M WINTER, JONATHAN BRODY	CASE WESTERN RESERVE UNIVERSITY
R01CA287866	Leveraging CD26high Meso-CAR T cells in patients with advanced pancreatic cancer	GREGORY B. LESINSKI, CHRYSTAL MARY PAULOS, EDMUND K WALLER	EMORY UNIVERSITY

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R01CA288145	Targeted EGFR for basal subtype pancreatic cancer	JEN JEN YEH, GARY L. JOHNSON	UNIV OF NORTH CAROLINA CHAPEL HILL
R01CA288617	TROP2-Directed CAR-NK Cells for the Immunotherapy of Pancreatic Cancer	RAFET BASAR, HIND RAFEI, KATY REZVANI	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA289249	Multimodal AI Fusion Model for Early Detection for Pancreatic Cancer	BHAVIK NATVAR PATEL, IMON BANERJEE, YIFAN PENG	MAYO CLINIC ARIZONA
R01CA289924	Development of a theragnostic radiopharmaceutical for pancreatic cancer	KATHERINE W FERRARA	STANFORD UNIVERSITY
R01CA290400	Investigating hypoxia as a determinant of malignant fates in pancreas cancer	TUOMAS TAMMELA, MICHAEL HEMANN	SLOAN-KETTERING INST CAN RESEARCH
R01CA290435	DCE-MRI guided Neoadjuvant Chemotherapy for Borderline Resectable Pancreatic Cancer	HARRISON KIM, BASSEL EL-RAYES, ASHIQ MASOOD	UNIVERSITY OF ALABAMA AT BIRMINGHAM
R01CA290780	Metabolic regulation of immunosuppressive myeloid cells in the tumor microenvironment of pancreatic cancer.	YAQING ZHANG, BIN ZHENG	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R01CA290859	Lysosome Trapped FAP-Targeted Theranostics for Pancreatic Cancer	JERED C GARRISON, MANEESH JAIN	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R01CA290888	Causes and Consequences of Adenosine Signaling in Pancreatic Cancer	TIMOTHY R DONAHUE, CAIUS GABRIEL RADU, ZEV A WAINBERG	UNIVERSITY OF CALIFORNIA LOS ANGELES
R01CA292860	Genetically-engineered Bacteria Overcome Therapy Resistance	RALPH R WEICHSELBAUM, MARK MIMEE	UNIVERSITY OF CHICAGO
R01CA293602	Targeting HMGA1 Tumor-Stromal Networks in Pancreatic Carcinogenesis	LINDA M S RESAR, ELIZABETH M. JAFFEE	JOHNS HOPKINS UNIVERSITY
R01CA294584	Mechanisms of JAG1-mediated immune suppression in the pancreatic cancer microenvironment	LAN ZHOU	METHODIST HOSPITAL RESEARCH INSTITUTE
R01CA294647	ProAgio in Pancreatic Cancer	BASSEL EL-RAYES, ZHI-REN LIU	UNIVERSITY OF ALABAMA AT BIRMINGHAM
R01CA294653	Intersection of cytoskeletal regulation with tumor cell metabolism	GINA LYNN RAZIDLO, MARK A. MC NIVEN	MAYO CLINIC ROCHESTER
R01DK052913	Epigenomic Regulation in Pancreatic Cell Growth	RAUL A. URRUTIA, GWEN LOMBERK	MEDICAL COLLEGE OF WISCONSIN
R01DK117459	Magnetic Resonance (MR) Fingerprinting for Quantification of Pancreatic Tumor Microvasculature	ALEXANDER SAVIO RAMOS GUIMARAES	OREGON HEALTH & SCIENCE UNIVERSITY
R01DK120698	Chemical pancreatectomy for chronic pancreatitis and pancreatic cancer	GEORGE K. GITTES, FARZAD ESNI	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
R01DK123079	Unraveling the Role of NADPH Oxidase in Inflammation-associated Pancreatic Diseases	WEIQIN LU	UNIVERSITY OF TEXAS EL PASO
R01DK124342	Mechanisms of injury-induced pancreatic neoplasia	AGNIESZKA BEATA BIALKOWSKA	STATE UNIVERSITY NEW YORK STONY BROOK
R01DK124474	Mechanisms of Pancreatic Fibrosis	RODGER A. LIDDLE	DUKE UNIVERSITY

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R01DK132631	A Pilot Clinical Trial of Paricalcitol for Chronic Pancreatitis	STEPHEN J. PANDOL, MARC T GOODMAN	CEDARS-SINAI MEDICAL CENTER
R01DK133393	Immune crosstalk through shared LN drainage in the digestive system	DARIA ESTERHAZY	UNIVERSITY OF CHICAGO
R01DK138473	Blood flow crosstalk between the endocrine and exocrine pancreas	MANAMI HARA, NARUTOSHI HIBINO	UNIVERSITY OF CHICAGO
R01DK138632	Investigating mechanisms underlying diabetes associated with exocrine pancreas diseases	SEUNG K KIM, PATRICK MACDONALD	STANFORD UNIVERSITY
R01EB017270	Chemophototherapy with Porphyrin-phospholipid Liposomes Permeabilized by Red Light	JONATHAN F LOVELL	STATE UNIVERSITY OF NEW YORK AT BUFFALO
R01EB020125	Theranostic Nanoparticles For Detection and Treatment of Pancreatic Cancer	LACEY R MCNALLY	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R01EB025173	Endoscopic Fine-Needle Light Scattering Spectroscopy for Pancreatic Cyst Diagnosis and Evaluation of Malignant Potential	LEV T PERELMAN	BETH ISRAEL DEACONESS MEDICAL CENTER
R01EB025990	Deployable Ultrasound Applicators for MRI Guided Thermal Therapy of Pancreatic Cancer	CHRIS JOHN DIEDERICH	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01EB030494	Patient-specific, high-sensitivity spectral CT for assessment of pancreatic cancer	PETER B NOËL, JIANAN GRACE GANG	UNIVERSITY OF PENNSYLVANIA
R01EB032337	Surrogate biomarkers for assessing changes in pancreatic cancer tumor microenvironment	MARVIN M DOYLEY	UNIVERSITY OF ROCHESTER
R01EB032801	Fully Quantitative Low-Dose, Motion-Resolved Dynamic Contrast-Enhanced MRI in Pancreatic Adenocarcinoma	ANTHONY G CHRISTODOULOU, DEBIAO LI	CEDARS-SINAI MEDICAL CENTER
R01EB032825	Artificial Intelligence powered virtual digital twins to construct and validate AI automated tools for safer MR-guided adaptive RT of abdominal cancers	NEELAM TYAGI, HARINI VEERARAGHAVAN	SLOAN-KETTERING INST CAN RESEARCH
R01EB034306	Multifunctional Biodegradable Zwitterionic Polymer-Drug Conjugates for Multidrug Co-Delivery	CHONG CHENG	STATE UNIVERSITY OF NEW YORK AT BUFFALO
R01EB034360	Molecular Imaging Guidance for Potentiating Chemoimmunotherapy in Pancreatic Cancer using Photodynamic Priming	GIRGIS OBAID	UNIVERSITY OF TEXAS DALLAS
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.	YONG ZHOU	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
R01GM143329	PR55-alpha controlled PP2A in the regulation of the Hippo/YAP pathway	YING YAN	UNIVERSITY OF NEBRASKA MEDICAL CENTER

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R01GM144450	Legumain to the rescue: A new ADC linker strategy to address the limitations of cathepsin cleavage	LAWRENCE TUMEY	STATE UNIVERSITY OF NY,BINGHAMTON
R01HL173340	Pulmonary and pancreatic response to cystic fibrosis modulator therapy in young children	ARLENE A STECENKO, RISHIKESAN KAMALESWARAN	EMORY UNIVERSITY
R01LM013902	Modeling and targeting tumor-immune signaling interactions in tumor microenvironment	FUHAI LI	WASHINGTON UNIVERSITY
R01MD019684	Examining the determinants and consequences of supportive care medication use disparities in patients with pancreatic cancer: A sequential mixed-methods approach	JOHN M ALLEN	UNIVERSITY OF FLORIDA
R03CA241971	Epigenetic Regulation of Hemidesmosome Signaling in Pancreatic Cancer	ANDREW LISS	MASSACHUSETTS GENERAL HOSPITAL
R03CA249401	Combining Immunotherapy with Urolithin A to Improve Pancreatic Cancer Survival	NAGARAJ S. NAGATHIHALLI	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
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	DALI SUN	NORTH DAKOTA STATE UNIVERSITY
R03CA262490	Evaluation of the antitumorigenic roles of miR-122 in pancreatic cancer	RAJGOPAL GOVINDARAJAN	OHIO STATE UNIVERSITY
R03CA267449	Using photopolymerizable collagen matrices to investigate how progressive stiffening alters lymphatic trafficking of cancer and immune cells in pancreatic ductal adenocarcinoma	CATHERINE F WHITTINGTON	WORCESTER POLYTECHNIC INSTITUTE
R03CA273479	Pancreatic adenocarcinoma secretome as a dynamic biomarker for patient stromal reprogramming efficacy	PAUL MICHAEL CAMPBELL	RESEARCH INST OF FOX CHASE CAN CTR
R03CA283232	Elucidating the relevance of BARD1-PLK1 interaction in PDAC and response to therapy	ADITI JAIN	THOMAS JEFFERSON UNIVERSITY
R03CA286643	Discovery of SATB2 Inhibitors for Pancreatic Cancer	RAKESH K. SRIVASTAVA	GLAX, LLC
R03CA286703	Enhancing intratumoral T cell infiltration by deliver of shCXCL5 in a Plectin targeted AAV to improve checkpoint blockade efficacy	MICHAEL NATHAN VANSAUN	UNIVERSITY OF KANSAS MEDICAL CENTER
R03CA289854	Uncoupling Ral signal transduction from Exocyst functions	DAVID REINER	TEXAS A&M UNIVERSITY HEALTH SCIENCE CTR
R03CA292973	Role of JMJD4 in Pancreatic Cancer	RALF JANKNECHT	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR

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R03TR003639	Nanobody inhibitors of proton-sensing G protein-coupled receptors	GEOFFREY A CHANG, PAUL A INSEL	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R03TR004473	PIP5K1A is a novel mutant KRAS effector and essential for pancreatic cancer cell survival	SUYONG CHOI	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R13AA020691	International Symposium of ALPD and Cirrhosis	HIDEKAZU TSUKAMOTO	UNIVERSITY OF SOUTHERN CALIFORNIA
R13CA265018	Africa Hepatopancreatobiliary Cancer Consortium	LEWIS R ROBERTS	MAYO CLINIC ROCHESTER
R13CA281305	2023 Pancreatic Diseases Gordon Research Conference and Gordon Research Seminar	NABEEL EL-BARDEESY	GORDON RESEARCH CONFERENCES
R13DK130515	PancreasFest 2021	DAVID CLEMENT WHITCOMB	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
R13DK137547	PancreasFest 2023	RANDALL BRAND	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
R13DK141076	PancreasFest 2024	MAISAM ABU-EL-HAIJA	CINCINNATI CHILDRENS HOSP MED CTR
R15CA238864	Rational Oncolytic Virotherapy For Pancreatic Cancer Using Vesicular Stomatitis Virus	VALERY ZURABOVICH GRDZELISHVILI	UNIVERSITY OF NORTH CAROLINA CHARLOTTE
R15CA249714	GSTP1 as a therapeutic target for pancreatic cancer	KATIE REINDL	NORTH DAKOTA STATE UNIVERSITY
R15CA267836	Characterizing the fibrogenic role of NADPH oxidase 1 in the transition from chronic pancreatitis to pancreatic cancer	MARIA EUGENIA SABBATINI	AUGUSTA UNIVERSITY
R15CA280729	Understanding and improving novel oncolytic viruses for pancreatic cancer	VALERY ZURABOVICH GRDZELISHVILI	UNIVERSITY OF NORTH CAROLINA CHARLOTTE
R15EB026208	Optimization of aminolevulinic acid-protoporphyrin IX for fluorescence-guided tumor resection and treatment	BIN CHEN	UNIVERSITY OF THE SCIENCES PHILADELPHIA
R16GM145556	Combination of tumor targeted therapy with stroma modulating agent for PDAC	KETANKUMAR D. PATEL	ST. JOHN'S UNIVERSITY
R16GM146714	Characterization of polyamine biosynthetic enzymes from human gut microbes associated with colon and pancreatic cancer	JEFFREY S MCFARLANE	FORT LEWIS COLLEGE
R16GM149427	MBQ-167 derivatives as antimetastatic cancer agents.	SURANGANIE DHARMAWARDHANE	UNIVERSITY OF PUERTO RICO MED SCIENCES
R21AG087544	The Aging Pancreas as a Pro-tumorigenic Niche	COSIMO COMMISSO	SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE
R21CA219899	PET Imaging of the Tumor Microenvironment for Cancer Detection	THADDEUS J. WADAS	UNIVERSITY OF IOWA
R21CA223403	A pre-clinical x-ray/optical tomography-guided radiation research platform for pancreatic cancer	KEN KANG-HSIN WANG, PHUOC T. TRAN	UT SOUTHWESTERN MEDICAL CENTER
R21CA224280	3D biomimetic image-based stromal models of pancreatic cancer for drug screening	PAUL J CAMPAGNOLA, MELISSA CAROLINE SKALA	UNIVERSITY OF WISCONSIN-MADISON

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R21CA227416	Phospholipase D1 and pancreatic cancer	GERARDO GUILLERMO MACKENZIE	UNIVERSITY OF CALIFORNIA AT DAVIS
R21CA234775	Large-scale proteome-wide analysis with high accuracy/precision to guide pancreatic cancer therapy development	ROBERT M STRAUBINGER, DONALD E MAGER, JUN QU	STATE UNIVERSITY OF NEW YORK AT BUFFALO
R21CA236561	Single Circulating Vesicle Analysis for Early Cancer Detection	MD WEISSLEDER	MASSACHUSETTS GENERAL HOSPITAL
R21CA236612	A microfluidic cell culture platform for personalizing pancreatic cancer therapies	ALEXANDER REVZIN	MAYO CLINIC ROCHESTER
R21CA236640	T-cell Biofactories for targeting interstitial fluid pressure	PARIJAT BHATNAGAR	SRI INTERNATIONAL
R21CA238953	Altered Histidine Metabolism in Pancreatic Cancer: A Novel Metabolic Target to Enhance Gemcitabine Efficacy	SARASWATHI VISWANATHAN, SATYANARAYANA RACHAGANI	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
R21CA244167	Smoking carcinogen-induced initiation of pancreatic cancer	PETER STORZ	MAYO CLINIC JACKSONVILLE
R21CA245437	Identify tumor suppressor driver genes of pancreatic ductal adenocarcinoma	PEI WANG	UNIVERSITY OF TEXAS HLTH SCIENCE CENTER
R21CA246550	Parametric optimization of ultrasound-mediated immuno-modulation for pancreatic cancer therapy	PAUL A DAYTON, YULIYA PYLAYEVA-GUPTA	UNIV OF NORTH CAROLINA CHAPEL HILL
R21CA248122	Inference of tumor growth dynamics using genomic data	SUBHAJYOTI DE	RBHS -CANCER INSTITUTE OF NEW JERSEY
R21CA249647	Coded-aperture Compton scatter imaging for real-time tumor motion tracking during ablative radiotherapy	BERNARD L JONES	UNIVERSITY OF COLORADO DENVER
R21CA249649	Tumor-permeable nanoparticles for enhanced pancreatic cancer immunochemotherapy	JINGJING SUN	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
R21CA251151	PROTACs for pancreatic cancer therapy	AMARNATH (AMAR) NATARAJAN	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R21CA252156	*In situ* cancer cell specific synthesis of gold nanoclusters for radiosensitization of pancreatic cancer	KONSTANTIN V SOKOLOV, SUNIL KRISHNAN	UNIVERSITY OF TX MD ANDERSON CAN CTR
R21CA252162	A Bioengineered Model of Tumor Vessel Interactions in Pancreatic Cancer	ESAK LEE	CORNELL UNIVERSITY
R21CA252535	Neoadjuvant Stroma Modification in Pancreatic Cancer	IGOR ASTSATUROV, EFRAT DOTAN	RESEARCH INST OF FOX CHASE CAN CTR
R21CA252585	Targeting Cell Cycle Plasticity in Pancreatic Ductal Adenocarcinoma	CHONGMIN HUAN, ERIK KNUDSEN	SUNY DOWNSTATE MEDICAL CENTER
R21CA253673	Microbiota pancreas interactions during cancer	JUNE LOUISE ROUND, LEWIS C MURTAUGH	UNIVERSITY OF UTAH

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R21CA255291	Rapid evaluation of immunotherapy regimens in ex vivo human pancreatic tumor slice cultures.	HIDAYATULLAH G. MUNSHI	NORTHWESTERN UNIVERSITY AT CHICAGO
R21CA256409	Mediators of Pancreatic Cancer-Associated Cachexia	ZOBEIDA CRUZ-MONSERRATE	OHIO STATE UNIVERSITY
R21CA257972	Sex-dependent rescue of cancer cachexia	ERIN E TALBERT	UNIVERSITY OF IOWA
R21CA258125	Interaction between Chronic Stress and Obesity in Pancreatic Cancer Progression	JUAN ENRIQUE ROZENGURT, GUIDO ERWIN MICHAEL EIBL	UNIVERSITY OF CALIFORNIA LOS ANGELES
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	RAHUL SURESH SHINDE	WISTAR INSTITUTE
R21CA263132	DNA methylation, Liquid Biopsy, and Pancreatic Cancer	MARK ANTHONY NELSON, BERNARD W FUTSCHER, RACHNA SHROFF	UNIVERSITY OF ARIZONA
R21CA263285	Developing ATAC-array as a novel epigenetic biomarker to guide personalized therapy in pancreatic cancer	STEVEN D LEACH	DARTMOUTH COLLEGE
R21CA263430	Operationalizing DNMT1-Targeting to Treat Chemorefractory Pancreatic Cancer	YOGEN SAUNTHARARAJAH	CLEVELAND CLINIC LERNER COM-CWRU
R21CA263462	Microbiota-mediated enhancement of the anti-tumor effect of natural killer cells	RYAN M. THOMAS, CHRISTIAN JOBIN	UNIVERSITY OF FLORIDA
R21CA263694	Biodegradable liquid metal nanoagents for photoacoustic image-guided photodynamic therapy	SRIVALLEESHA MALLIDI	TUFTS UNIVERSITY MEDFORD
R21CA263996	Developing a patient derived model platform to treat BRCA1/2-mutant pancreatic cancers	JONATHAN BRODY, ROSALIE C SEARS	OREGON HEALTH & SCIENCE UNIVERSITY
R21CA264004	Immunophenotype Integration for Monitoring T Cell Dynamics in Pancreatic Cancers	WON JIN HO	JOHNS HOPKINS UNIVERSITY
R21CA264339	A deep-transfer-learning framework to transfer clinical information to single cells and spatial locations in cancer tissues	TRAVIS STEELE JOHNSON, JIE ZHANG	INDIANA UNIVERSITY INDIANAPOLIS
R21CA265400	Domain-Knowledge Informed Deep Learning for Early Detection of Pancreatic Cancer	CHIN HUR, NICHOLAS P TATONETTI	COLUMBIA UNIVERSITY HEALTH SCIENCES
R21CA266088	Modulation of the human pancreatic microenvironment by combined cytokine and immune checkpoint blockade	GREGORY B. LESINSKI, BASSEL EL-RAYES	EMORY UNIVERSITY
R21CA267124	Integrated Genomic-Transcriptomic Characterization to Identify Molecular Mechanisms of Disparities in PDAC Outcomes	VIKAS DUDEJA	UNIVERSITY OF ALABAMA AT BIRMINGHAM

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R21CA267302	Mechanisms of anti-tumor activity of group A Streptococcus in pancreatic adenocarcinoma	BRIAN A BOONE, SLAWOMIR LUKOMSKI	WEST VIRGINIA UNIVERSITY
R21CA267803	A novel gene therapy approach targeting STING-silenced cold tumors	JIANXIN YOU	UNIVERSITY OF PENNSYLVANIA
R21CA270588	ULK1 Inhibitor in Combination with Immune Checkpoint Blockade in PancreaticCancer	JEFFREY PAUL MACKEIGAN	MICHIGAN STATE UNIVERSITY
R21CA270748	Exosomal Contents Guided Amino Acids Treatment for Pancreatic Cancer	DALI SUN	UNIVERSITY OF DENVER (COLORADO SEMINARY)
R21CA273506	A novel small molecule targeting protein translation for pancreatic cancer treatment	GERARDO GUILLERMO MACKENZIE, RUIWU LIU	UNIVERSITY OF CALIFORNIA AT DAVIS
R21CA273973	Targeting the MICAL2 signaling axis in pancreatic cancer	ANDREW M LOWY	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R21CA273983	Engineering Siglec15/TGF-beta targeted bispecific antibodies that modulate the tumor microenvironment and enhances T-cell immunotherapy against pancreatic cancer	SAMUEL LAI	UNIV OF NORTH CAROLINA CHAPEL HILL
R21CA274425	PIK3CA signaling and pancreatic cancer	RICHARD Z LIN	STATE UNIVERSITY NEW YORK STONY BROOK
R21CA277110	Personalized Organoid-Chip Model For Drug Testing in Pancreatic Cancer	FARAZ BISHEHSARI	RUSH UNIVERSITY MEDICAL CENTER
R21CA277250	DNASE1L3 regulation of anti-tumor immune responses following radiation therapy	MICHAEL JAMES GOUGH	PROVIDENCE HEALTH & SERVICES - OREGON
R21CA277464	Managing metabolic disruption in pancreatic cancer to prevent weight loss and improve quality of life	JAMES H FLORY	SLOAN-KETTERING INST CAN RESEARCH
R21CA279916	Deiminated molecules as markers for developing pancreatic cancer - A1	PETER STORZ	MAYO CLINIC JACKSONVILLE
R21CA283420	Engineered exosome mimetics as targeted biological nanomedicines for pancreatic cancer	MARSHA A MOSES	BOSTON CHILDREN'S HOSPITAL
R21CA283492	Development of a clinically relevant mouse model of lung cancer cachexia to study pathoetiology and therapeutic strategies	MICHAEL J TOTH	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
R21CA286198	Harnessing Cytomegalovirus (CMV)-specific T-cells for pancreatic cancer immunotherapy	TATIANA HURTADO DE MENDOZA, CHRISTOPHER A BENEDICT	UNIVERSITY OF CALIFORNIA, SAN DIEGO
R21CA286283	Development of a PET CCR2 Imaging Agent to Profile PDAC Microenvironment	MARK MYRON GOODMAN, GREGORY B. LESINSKI	EMORY UNIVERSITY
R21CA286348	Inhibition of pleiotrophin to combat pancreatic cancer metastasis	ROLF A BREKKEN	UT SOUTHWESTERN MEDICAL CENTER
R21CA286398	Develop universal CAR macrophage cell therapy for pancreatic cancer	PINGPING HOU	RUTGERS BIOMEDICAL AND HEALTH SCIENCES
R21CA288671	Genomic lineage traces as biomarkers for human pancreatic and liver cancer	LEWIS C MURTAUGH	UNIVERSITY OF UTAH

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R21CA288804	A Novel Strategy of Targeting Transmembrane Protein to Improve KRAS-targeted Therapy	WANTONG YAO	UNIVERSITY OF TX MD ANDERSON CAN CTR
R21CA292190	Monitoring Listeria *in vivo* using 18FDG and PET scan	CLAUDIA GRAVEKAMP	ALBERT EINSTEIN COLLEGE OF MEDICINE
R21EB028429	Employing Novel Porcine Models of Orthotopic Pancreatic Cancer to Evaluate Histotripsy Based Tumor Ablation Strategies	IRVING C ALLEN	VIRGINIA POLYTECHNIC INST AND ST UNIV
R21EB028508	Photodynamic Priming for Bidirectional Modulation of Drug Transport Across the Blood-Brain Tumor Barrier	HUANG CHIAO HUANG	UNIV OF MARYLAND, COLLEGE PARK
R33CA206907	Rapid unbiased isolation and *in situ* RNA analysis of circulating tumor cells using a magnetic micropore-based diagnostic chip	DAVID AARON ISSADORE	UNIVERSITY OF PENNSYLVANIA
R33CA229068	Advanced Development of the MasSpec Pen for Cancer Diagnosis and Surgical Margin Evaluation	LIVIA SCHIAVINATO EBERLIN	BAYLOR COLLEGE OF MEDICINE
R33CA278551	Combining Machine Learning and Nanofluidic Technology for The Multiplexed Diagnosis of Pancreatic Adenocarcinoma	DAVID AARON ISSADORE, ERICA CARPENTER	UNIVERSITY OF PENNSYLVANIA
R33CA287135	High Throughput Digital Droplet Assays for Ultrasensitive Multimodal (DNA, RNA, and Protein) Diagnostics	DAVID AARON ISSADORE	UNIVERSITY OF PENNSYLVANIA
R35CA197566	Mechanisms governing metastatic dormancy and reactivation	FILIPPO G GIANCOTTI	COLUMBIA UNIVERSITY HEALTH SCIENCES
R35CA197699	Molecular strategies for early detection and targeting of cancer	TANNISHTHA REYA	COLUMBIA UNIVERSITY HEALTH SCIENCES
R35CA197709	New Ways of Targeting K-Ras	FRANK PATRICK MCCORMICK	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R35CA209960	Molecular Imaging and Theranostics of Cancer	ZAVER M. BHUJWALLA	JOHNS HOPKINS UNIVERSITY
R35CA232113	Targeting undruggable RAS for cancer treatment	CHANNING J. DER	UNIV OF NORTH CAROLINA CHAPEL HILL
R35CA232124	Identifying Metabolic Dependencies of Pancreatic Cancers	ALEC KIMMELMAN	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R35CA263815	Biology and Function of Exosomes in Cancer	RAGHU KALLURI	UNIVERSITY OF TX MD ANDERSON CAN CTR
R35CA274464	Studying factors controlling cancer progression and immune recognition in mouse models	TYLER E. JACKS	MASSACHUSETTS INSTITUTE OF TECHNOLOGY
R35GM127030	Chemical tools for developmental biology	JAMES K CHEN	STANFORD UNIVERSITY
R35GM131800	Mechanistic Pharmacokinetics and Pharmacodynamics	WILLIAM J. JUSKO	STATE UNIVERSITY OF NEW YORK AT BUFFALO
R35GM138335	Tools to Study Electrophilic Stress and Develop Covalent Drugs	RAPHAEL M. FRANZINI	UNIVERSITY OF UTAH
R35HL155657	Tissue factor-dependent coagulation in thrombosis and immune responses	NIGEL MACKMAN	UNIV OF NORTH CAROLINA CHAPEL HILL

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R37CA214679	Multi-site Gastrointestinal Cancer Detection by Stool DNA Methylation	JOHN KISIEL	MAYO CLINIC ROCHESTER
R37CA219697	IRAK4 AS A NOVEL IMMUNOTHERAPEUTIC TARGET IN PANCREATIC DUCTAL ADENOCARCINOMA	KIAN H LIM	WASHINGTON UNIVERSITY
R37CA222215	Combined radiation acoustics and ultrasound imaging for real-time guidance in radiotherapy	ISSAM M. EL NAQA	H. LEE MOFFITT CANCER CTR & RES INST
R37CA227865	Targeting pancreatic cancer's metabolic addiction to HuR	JORDAN M WINTER	CASE WESTERN RESERVE UNIVERSITY
R37CA229417	Spacer Enabled Robust Radiation Therapy (SERRT)	KAI DING	JOHNS HOPKINS UNIVERSITY
R37CA230786	Function of IL35+ B cells in pancreatic cancer	YULIYA PYLAYEVA-GUPTA	UNIV OF NORTH CAROLINA CHAPEL HILL
R37CA234006	Novel Nanomedicine-Based Therapeutic Approach For Treatment of Cancer Cachexia	OLEH TARATULA	OREGON STATE UNIVERSITY
R37CA237384	Dissecting the source and mechanisms of IL-17-mediated modulation of pancreatic tumorigenesis	FLORENCIA MCALLISTER	UNIVERSITY OF TX MD ANDERSON CAN CTR
R37CA237421	Intratumoral Metabolic Crosstalk Promotes Therapeutic Resistance in Pancreatic Cancer	COSTAS ANDREAS LYSSIOTIS	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R37CA240765	Cancer under pressure: Mechanisms of adaptation to compressive stress	LIAM J HOLT	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R37CA241472	Exploring the epigenetic control of pancreatic cancer subtypes	SITA KUGEL	FRED HUTCHINSON CANCER CENTER
R37CA242070	Targeting tumor architecture as a novel therapeutic strategy for pancreatic cancer	MATTEO LIGORIO	UT SOUTHWESTERN MEDICAL CENTER
R37CA244911	Targeting stem-like cells and their niche in pancreatic cancer	TUOMAS TAMMELA	SLOAN-KETTERING INST CAN RESEARCH
R37CA249007	Engrailed-1 and Epigenetic Vulnerabilities in Metastatic Pancreatic Cancer	CHANG-IL HWANG	UNIVERSITY OF CALIFORNIA AT DAVIS
R37CA251877	Mechanistic dissection and inhibitor targeting of autophagy in RAS driven cancers	KIRSTEN L BRYANT	UNIV OF NORTH CAROLINA CHAPEL HILL
R37CA252305	Regulation of tumor suppression by alpha-ketoglutarate	LYDIA FINLEY	SLOAN-KETTERING INST CAN RESEARCH
R37CA258787	Distinguishing Pancreatic Cancer from Benign Pancreatic Disease using Nanoparticle-based Biomarkers	STUART DUNCAN IBSEN	OREGON HEALTH & SCIENCE UNIVERSITY
R37CA262209	Defining epigenetic signaling to reshape pancreatic tumor microenvironment	JIAQI SHI	UNIVERSITY OF MICHIGAN AT ANN ARBOR
R37CA272744	Targeting Acquired Resistance in KRAS Driven Cancers	WANTONG YAO	UNIVERSITY OF TX MD ANDERSON CAN CTR
R37CA275961	Targeting HNF1A-mediated therapeutic resistance in pancreatic ductal adenocarcinoma	ETHAN VINCENT ABEL	ROSWELL PARK CANCER INSTITUTE CORP

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R37CA276924	Vitamin B6 Modulates NK Cell Metabolism in Pancreatic Cancer	KAMIYA MEHLA	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R37CA280692	Metabolic vulnerability due to dysregulated lipid metabolism in PDAC cachexia	AARON GROSSBERG	OREGON HEALTH & SCIENCE UNIVERSITY
R37CA280869	Characterizing the sources, mechanisms, and translational relevance of microbial TMAO in driving anti-tumor immunity in pancreatic cancer.	RAHUL SURESH SHINDE	WISTAR INSTITUTE
R37CA283575	Targeting Metabolic Crosstalk in Pancreatic Cancer	CHRISTOPHER J. HALBROOK	UNIVERSITY OF CALIFORNIA-IRVINE
R37CA285640	Uncovering Oncogenotype-specific Vulnerabilities in Lung cancer	JIYEON KIM	YALE UNIVERSITY
R37CA289040	Elucidating The Adaptive Role Of Serine Codons During Pancreatic Tumorigenesis	ROBERT SINGHUNG BANH	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R37CA292056	Mutant KRAS targeted vaccines for the interception of pancreatic cancer development	NEEHA ZAIDI	JOHNS HOPKINS UNIVERSITY
R37CA292781	Systems Metabolic Approach for Multi-scale Pancreatic Cancer Phenotyping	NEEMA JAMSHIDI	UNIVERSITY OF CALIFORNIA LOS ANGELES
R37CA292843	Disrupting MDSC-fibroblast interactions to overcome chemoimmunotherapy resistance in pancreatic cancer	JASHODEEP DATTA	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
R41CA247165	Tumor Stroma Breaking System for Efficient Delivery of Therapeutic Agents	LILY YANG, H TRENT SPENCER, LEI ZHU	MIGRA-THERAPEUTICS, LLC
R41CA250892	Modulation of the gut microbiome to enhance efficacy of immunotherapy in pancreatic adenocarcinoma	DEEPAK SAXENA, XIN LI	PERIOMICS CARE, LLC
R41CA254492	Development of a Targeted Radiotherapeuitc for Pancreatic Ductal Adenocarcinoma	JERED C GARRISON	ADDUCTNE, LLC
R41CA254746	Small molecule inhibitors of oncogenic miR-21	GABRIELE VARANI, GEORGE A. CALIN	ITHAX PHARMACEUTICALS, INC.
R41CA265512	A novel monobody-drug conjugate to treat mutant KRas pancreatic cancer.	CRAIG PATRICK RAMIREZ, DAFNA BAR-SAGI, SHOHEI KOIDE	TEZCAT LABORATORIES LLC
R41CA265619	The use of tMUC1/CD3 bispecific antibody to control pancreatic ductal adenocarcinoma	PINKU MUKHERJEE, RU ZHOU	ONCOTAB, INC
R41CA265624	Bispecific T cell engagers for the treatment of pancreatic ductal adenocarcinoma	NATHAN G. DOLLOFF	LEUKOGENE THERAPEUTICS, INC.
R41CA265655	An integrated strategy using a serum and imaging biomarker for the early detection of pancreatic cancer.	PINKU MUKHERJEE, RU ZHOU	ONCOTAB, INC
R41CA275619	Targeting cadherin-11 in pancreatic cancer	SIVANESAN DAKSHANAMURTHY	DIVINER THERAPEUTICS, LLC
R41CA275625	Development of (R,S')-MNF as a dual-targeted therapy for pancreatic cancer	IRVING WAINER, HAIYONG HAN	PAZ PHARMACEUTICALS

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R41CA278033	Stroma-penetrating nanomedicine to improve treatment for pancreatic cancer	KATHERINE MARIE EICHINGER	DUO ONCOLOGY INC
R41CA285174	A novel dual-carrier ultrasmall nanomedicine for the treatment of stroma-rich pancreatic cancer	KATHERINE MARIE EICHINGER	DUO ONCOLOGY INC
R41CA287830	Precision medicine for pancreatic cancer. Biomarker-guided drug delivery of platinum to tumors	NICHOLAS PATRICK FARRELL, JOSE G. TREVINO	BIOPLATINUM TECHNOLOGIES, LLC
R42CA239853	Preclinical Development of ACXT-3102 for the Treatment of Pancreatic Adenocarcinoma (PDAC)	BRADLEY T KELLER, WILLIAM G HAWKINS	ACCURONIX THERAPEUTICS, INC.
R42CA265691	SIRPant Technology for anti-Cancer Immunity	NATHANAEL MCCURLEY	SIRPANT IMMUNOTHERAPEUTICS, INC.
R42CA268138	AGR2-superantigen vaccine conjugate for the treatment of pancreaticductal adenocarcinoma	REEDER MCNEIL ROBINSON	LEUKOGENE THERAPEUTICS, INC.
R42CA287679	Clinical testing of Listeria-TT and Gemcitabine in a Phase 1 clinical trial with PDAC patients	CHRIS BRADLEY, CLAUDIA GRAVEKAMP, CHAOYUAN KUANG, JOHN MCAULIFFE	LOKI THERAPEUTICS, INC
R43CA221602	Development of a vault nanovaccine for pancreatic cancer immunotherapy	GAYLE BOXX	AUKERA, INC.
R43CA246827	Translational Development of a Targeted and Stroma-breaking Nanoparticle Drug for Pancreatic Cancer Therapy	LEI ZHU, LILY YANG	MIGRA-THERAPEUTICS, LLC
R43CA250780	OPN neutralization monoclonal antibody 100G2 for human pancreatic cancer immunotherapy	PRISCILLA SIMON REDD	CHEMEDIMMUNE, INC.
R43CA254794	MyD88 fusion protein with antigen specific T Cell therapy for enhanced response in solid tumors	SAMANTHA DUNMIRE	LUMINARY THERAPEUTICS, INC.
R43CA254820	Simultaneous Targeting of Tumor and Stroma Cells to Enhance Solid Tumor CAR-T Cell Therapy	NICOLE J. SHIRKEY-SON	LUMINARY THERAPEUTICS, INC.
R43CA261286	A novel T cell subset with increased potency and persistence for the treatment of solid tumors	BRIAN NEWSOM	ARES IMMUNOTHERAPY, INC.
R43CA272110	Sub-100 nm and scalable self-therapeutic nanoparticles to target autophagy in pancreatic cancer	TZU-YIN LIN	THERANOSTEC, INC.
R43CA275410	Perform non-GLP and GLP TOX/TK studies, and file a novel drug IND with the FDA for advanced pancreatic cancer patient clinical trials	XIANG LING, FENGZHI LI	CANGET BIOTEKPHARMA, LLC
R43CA275458	Optimization of TIL Cell Manufacturing for Cancer Treatment	SOON SEOG JEONG	HUMAN CELL CO
R43CA277913	Translational Assays for Inflammatory Biomarkers for the Risk Stratification of Pancreatic Cystic Lesions	DANIEL SHEIK	AMPLIFIED SCIENCES INC
R43CA277917	Targeting pancreatic cancer metastases with Targefrin	CARLO BAGGIO	ARMIDA LABS, INC.

Project Number	Title	Principal Investigator(s)	Institution
R43CA278168	Integration of non-invasive deep tissue microwave thermometry in the VectRx hyperthermia device in a transgenic liver tumor pig model	PIERRE N FLORIANO	NEOTHERMA ONCOLOGY, INC.
R43CA281460	An Aptamer-directed IgG1-Fc Drug Conjugate (AFDC) for Treating Pancreatic Cancer	XIANG GAO	ONCOTRAP, INC.
R44CA199058	A Prognostic Blood Test to Monitor Pancreatic Cancer Treatment by MiRNA Profiling	RAVI SARAF	VAJRA INSTRUMENTS, INC.
R44CA203336	Immuno-Oncology for Pancreatic Cancer: A Combination Clinical Trial with Chemotherapy and Radiation	ESTUARDO AGUILAR-CORDOVA, LAURA K AGUILAR	ADVANTAGENE, INC
R44CA210770	Commercializing CivaSheet for Pancreatic Cancer Patients	KRISTY PEREZ	CIVATECH ONCOLOGY, INC.
R44CA217400	First-in-class TREM-1 inhibitors in combination therapy for pancreatic cancer	ALEXANDER B SIGALOV	SIGNABLOK, INC.
R44CA221374	Generation of antibody-drug conjugates by proximity-based sortase-mediated ligation	FEIFAN YU	ALPHATHERA, INC.
R44CA224460	Implantable iontophoresis chemotherapy delivery device for direct infusion ofgemcitabine into pancreatic adenocarcinoma: Device development and First-in-Human clinical trial	WILLIAM ANDREW DAUNCH	FOCAL MEDICAL, INC.
R44CA224472	Development of a DCLK1 siRNA Nanoparticle as Targeted Therapy to Treat Pancreatic Cancer	ELISEU O. DE OLIVEIRA, SRIPATHI M SUREBAN	COARE HOLDINGS, INC.
R44CA235991	Targeting LIF/LIFR in pancreatic cancer	HAREESH BABU NAIR, SUSHIL KUMAR	EVESTRA, INC.
R44CA246827	Translational Development of a Targeted and Stroma-penetrating Nanoparticle Drug for Pancreatic Cancer Therapy	LEI ZHU, LILY YANG, LINGXUN DUAN	MIGRA-THERAPEUTICS, LLC
R44CA250861	Ultra-high content analyses of circulating and solid tumor cells: A diagnostic reference system for disease burden	MICHEL NEDERLOF	QUANTITATIVE IMAGING SYSTEMS, LLC
R44CA265434	Development of Claudin MAbs for Treating Solid Tumors	JOSEPH BENJAMIN RUCKER	INTEGRAL MOLECULAR
R44CA268138	AGR2-superantigen vaccine conjugate for the treatment of pancreaticductal adenocarcinoma	REEDER MCNEIL ROBINSON	LEUKOGENE THERAPEUTICS, INC.
R44CA268403	Non-invasive staging of Metastasis by Precision MRI	YITING XU, JENNY J. YANG	INLIGHTA BIOSCIENCES, LLC
R44CA278026	Development of a Novel Resolvin-Based Therapy for Treatment of Pancreatic Cancer	JOHN PARKINSON	THETIS PHARMACEUTICALS, LLC
R44CA287653	Controlling Tumor Immune Escape in Pancreatic Cancer using a Dual T Cell Product Strategy	ERIC ANDREW SMITH	MARKER THERAPEUTICS, INC.
R44DK134212	A novel highly stable pancreatic enzyme replacement therapy to improve	ROBERT GALLOTTO, SHENDA BAKER	SYNSPIRA THERAPEUTICS, INC.

Project Number	Title	Principal Investigator(s)	Institution
	outcomes for patients with pancreatic insufficiency.		
R44GM128477	Development of a companion diagnostic to identify patients who respond to microbiome-targeting drugs	BRET DAVID WALLACE	SYMBERIX, INC.
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 AT ANN ARBOR
R50CA233186	The role of DCLK1 in the initiation of pancreatic ductal adenocarcinoma and colorectal cancer	DONGFENG QU	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
R50CA251836	Mutant p53 gain-of-function as an actionable target in cancer therapy	ALICE NEMAJEROVA	STATE UNIVERSITY NEW YORK STONY BROOK
R61CA278398	Program the Immune System against RAS-driven Cancer	XIAOJING J GAO, MONTE MEIER WINSLOW	STANFORD UNIVERSITY
S10OD025190	6 MeV/amu ion linac for deep-penetration microbeam and millimeter-beam charged-particle irradiations in small animals and biological tissues	DAVID JONATHAN BRENNER	COLUMBIA UNIVERSITY HEALTH SCIENCES
S10OD028498	Major upgrade for UAB Bruker BioSpec preclinical 9.4T MRI	ANNA C. SORACE	UNIVERSITY OF ALABAMA AT BIRMINGHAM
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	BILAL BIN HAFEEZ	UNIVERSITY OF TEXAS RIO GRANDE VALLEY
SC1GM144171	Priming pancreatic ductal adenocarcinoma using blood thinners to sensitize the efficacy of checkpoint immunotherapy	TASLIM A AL-HILAL	UNIVERSITY OF TEXAS EL PASO
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 B. HAAB, PETER J ALLEN, RANDALL BRAND	VAN ANDEL RESEARCH INSTITUTE
U01CA200468	Clinical Validation Center for Early Detection of Pancreatic Cancer	ANIRBAN MAITRA	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01CA210020	Molecular Imaging Methods for the Detection of Pancreatic Ductal Adenocarcinoma	ANDREI IAGARU, WALTER GWANG-UP PARK	STANFORD UNIVERSITY
U01CA210138	Mayo Clinic Prospective Resource for Biomarker Validation and Early Detection of Pancreatic Cancer	SHOUNAK MAJUMDER, KENNETH ZARET, GLORIA M. PETERSEN	MAYO CLINIC ROCHESTER

Project Number	Title	Principal Investigator(s)	Institution
U01CA210170	Using markers to improve pancreatic cancer screening and surveillance: a multi-center study	MICHAEL G. GOGGINS	JOHNS HOPKINS UNIVERSITY
U01CA210171	Altered metabolism and machine learning for pancreatic cancer early detection	BRIAN MATTHEW WOLPIN, MICHAEL H. ROSENTHAL	DANA-FARBER CANCER INST
U01CA213862	Nanovaccine platforms to combat pancreatic cancer	BALAJI NARASIMHAN, MANEESH JAIN, ALIASGER K SALEM	IOWA STATE UNIVERSITY
U01CA214263	Circulating Biomarkers and Imaging for Early Detection of Pancreatic Cancer	SUBRATA SEN, ANN M KILLARY, EUGENE J KOAY	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01CA216449	Sensitization to Chemoradiation by Therapeutic Targeting of the DNA Damage Response	THEODORE S LAWRENCE	UNIVERSITY OF MICHIGAN AT ANN ARBOR
U01CA216468	Enhancing Chemoradiation Efficacy through Unbiased Drug Discovery Approaches	STEVEN HSESHENG LIN, SUNIL KRISHNAN	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01CA217665	Peptide-based targeted molecular imaging for early detection in pancreatic cancer	JULIE L SUTCLIFFE	UNIVERSITY OF CALIFORNIA AT DAVIS
U01CA217842	Integrative bioinformatics and functional characterization of oncogenic driver aberrations in cancer	GORDON B. MILLS, BENJAMIN DENEEN, KENNETH L. SCOTT	OREGON HEALTH & SCIENCE UNIVERSITY
U01CA221046	Pretargeted Clinical Imaging of CA19.9 in Pancreatic Cancer	JASON S. LEWIS, BRIAN MATTHEW ZEGLIS	SLOAN-KETTERING INST CAN RESEARCH
U01CA224012	Comparative analysis between patient-derived models of pancreatic ductal adenocarcinomas and matched tumor specimens	ROSALIE C SEARS, JONATHAN BRODY, LISA M. COUSSENS, EMEK DEMIR	OREGON HEALTH & SCIENCE UNIVERSITY
U01CA224013	CSHL-JAX Patient-Derived Models of Pancreatic Cancer as Systems for Investigating Tumor Heterogeneity	DAVID A TUVESON, PAUL ROBSON	COLD SPRING HARBOR LABORATORY
U01CA224145	Interrupting Cellular Crosstalk in the Immunosuppressive Microenvironment of Pancreas Cancer	MARINA PASCA DI MAGLIANO, HOWARD C. CRAWFORD	UNIVERSITY OF MICHIGAN AT ANN ARBOR
U01CA224146	Systematic interrogation of the pancreatic cancer microenvironment in patient-derived specimens	WILLIAM C. HAHN	DANA-FARBER CANCER INST
U01CA224175	Defining neoantigen immunodominance for antigen selection and biomarker discovery in human pancreatic cancer immunotherapy	VINOD P BALACHANDRAN, STEVEN D LEACH	SLOAN-KETTERING INST CAN RESEARCH
U01CA224193	Disrupting the immune and drug-privileged microenvironment in pancreas cancer	SUNIL R HINGORANI	FRED HUTCHINSON CANCER CENTER
U01CA224348	Reprogramming PDAC tumor microenvironment to improve immunotherapy	RAKESH K. JAIN, YVES BOUCHER, MIKAEL PITTET	MASSACHUSETTS GENERAL HOSPITAL
U01CA226158	Subpopulations of Pancreatic Cancer Cells Defined by Glycan Markers	BRIAN B. HAAB, RANDALL BRAND	VAN ANDEL RESEARCH INSTITUTE

Project Number	Title	Principal Investigator(s)	Institution
U01CA233581	Sialylation-dependent mechanisms driving pancreatic cancer progression	SUSAN L BELLIS, LANCE WELLS	UNIVERSITY OF ALABAMA AT BIRMINGHAM
U01CA242936	Computational pathology software for integrative cancer research with three-dimensional digital slides	JUN KONG, FUSHENG WANG	GEORGIA STATE UNIVERSITY
U01CA243007	Optimal control models of epithelial-mesenchymal transition for the design of pancreas cancer combination therapy	MATTHEW J LAZZARA	UNIVERSITY OF VIRGINIA
U01CA243695	Development and Implementation of ElectronicDecision Aids for Genetic Testing in Inherited Cancer Syndromes	DANIEL C CHUNG	MASSACHUSETTS GENERAL HOSPITAL
U01CA247283	Multi-Ancestry Mapping of Pancreatic Cancer Susceptibility Loci	ALISON P KLEIN	JOHNS HOPKINS UNIVERSITY
U01CA250186	The Oral Mycobiome and Risk of Pancreatic Cancer	JIYOUNG AHN, RICHARD BERNARD HAYES	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
U01CA250549	Development and implementation of multiplex methods to understand the biology and heterogeneity of patient-derived cancer models	WILLIAM C. HAHN	DANA-FARBER CANCER INST
U01CA252965	Digital Nanoplasmonic Quantification of Tumor-derived Extracellular Vesicles in Plasma Microsamples	TONY Y. HU, HUA LU, SUBRATA SEN	TULANE UNIVERSITY OF LOUISIANA
U01CA265697	Synthetic circuits that drive infiltration of therapeutic T cells into immunologically cold tumors	WENDELL A LIM, HANA EL-SAMAD	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
U01CA271250	Advancing the Clinical Translation of Cyst Fluid Assays for Early Detection of Pancreatic Cancer	KIMBERLY SAUNDERS KIRKWOOD	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
U01CA274154	Fibroblast orchestration of the immune response in pancreatic cancer	MARINA PASCA DI MAGLIANO, HOWARD C. CRAWFORD, TIMOTHY LOUIS FRANKEL, COSTAS ANDREAS LYSSIOTIS	UNIVERSITY OF MICHIGAN AT ANN ARBOR
U01CA274276	Stromal modulation of pancreatic cancer malignant cell state and therapeutic sensitivity	WILLIAM C. HAHN, ANDREW JAMES AGUIRRE, STEPHANIE DOUGAN	DANA-FARBER CANCER INST
U01CA274295	Regulation of PDAC metabolism and immunity by collagen and its cleavage products	MICHAEL KARIN, ANDREW M LOWY, ROBERT F. SCHWABE	UNIVERSITY OF CALIFORNIA, SAN DIEGO
U01CA274304	Reprogramming PDAC Stroma by Targeting Coagulation in the Tumor Microenvironment	BUMSOO HAN, MELISSA L. FISHEL, MATTHEW J. FLICK	UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN
U01CA274312	Elucidation and targeting of paracrine cascades in PDAC	KENNETH P. OLIVE, GULAM ABBAS MANJI	COLUMBIA UNIVERSITY HEALTH SCIENCES
U01CA282269	Using microvolumetric cyst fluid proteolysis for early detection of pancreatic cancer	KIMBERLY SAUNDERS KIRKWOOD	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Project Number	Title	Principal Investigator(s)	Institution
U01CA284086	The Impact of Metastatic Site On Dendritic Cell-Driven Tumor Immunity	DAVID G DENARDO, LI DING, RYAN C FIELDS	WASHINGTON UNIVERSITY
U01CA293883	Uncovering Causal Protein Markers to Characterize Pancreatic Cancer Etiology and Improve Risk Prediction	LANG WU, CHONG WU	UNIVERSITY OF HAWAII AT MANOA
U01DK108288	The Exocrine and Endocrine Pancreas in Type 2 Diabetes, Pancreatitis and Cancer	SANTHI SWAROOP VEGE, SURESH T. CHARI, GLORIA M. PETERSEN, MARK D TOPAZIAN	MAYO CLINIC ROCHESTER
U01DK108300	The Stanford Clinical Center for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer	WALTER GWANG-UP PARK, AIDA HABTEZION, SEUNG K KIM	STANFORD UNIVERSITY
U01DK108306	Consortium for the study of chronic pancreatitis, diabetes and pancreatic cancer: Pittsburgh Clinical Center	DHIRAJ YADAV, RANDALL BRAND, DAVID CLEMENT WHITCOMB	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
U01DK108314	Greater Los Angeles Clinical Center of the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer	STEPHEN J. PANDOL, MARK GOODARZI	CEDARS-SINAI MEDICAL CENTER
U01DK108320	U-01 CONSORTIUM FOR THE STUDY OF CHRONIC PANCREATITIS,DIABETES AND PANCREATIC CANCER CLINICAL CENTERS	CHRISTOPHER E FORSMARK, KENNETH CUSI, STEVEN J HUGHES	UNIVERSITY OF FLORIDA
U01DK108323	Indiana University (IU) Clinical Center for Chronic Pancreatitis Clinical Research Network	EVAN L FOGEL	INDIANA UNIVERSITY INDIANAPOLIS
U01DK108326	DYSBIOTIC 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	PHILIP A. HART, DARWIN LEWIS CONWELL, HANNO STEEN, PETER ALAN BANKS, MELENA D. BELLIN, CHERYL E GARIEPY, FRANCIS G GRESS, JOSEPH PALERMO, MARK D TOPAZIAN, DAVID CLEMENT WHITCOMB, PAMELA G. BANKS, ANDRES GELRUD	OHIO STATE UNIVERSITY
U01DK108328	Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer: Coordinating and Data Management Center (CSCPDPC-CDMC)	YING YUAN, LIANG LI, ANIRBAN MAITRA, ZIDING FENG	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01DK126300	University of Minnesota Clinical Center for the Study of Pancreatic Disease	MELENA D. BELLIN, GREGORY J BEILMAN,	UNIVERSITY OF MINNESOTA

Project Number	Title	Principal Investigator(s)	Institution
		GURU V TRIKUDANATHAN	
U01DK126365	The Texas-Louisiana Alliance to Study Chronic Pancreatitis, Diabetes and Pancreatic Cancer	SURESH T. CHARI, ANIRBAN MAITRA	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01HL143365	Biomarkers and mechanisms in cancer associated thrombosis	ROBERT C FLAUMENHAFT, ELLIOT CHAIKOF, JEFFREY ZWICKER	BETH ISRAEL DEACONESS MEDICAL CENTER
U01HL143402	Novel approaches to improve prediction of cancer-associated thrombosis	KEITH R. MCCRAE, ALOK A KHORANA	CLEVELAND CLINIC LERNER COM-CWRU
U01HL143403	Targeting the Plasminogen Activation System to Limit Pancreatic Cancer Progression and Associated Thrombosis	MATTHEW J. FLICK, MELISSA L. FISHEL, BUMSOO HAN, ALISA S. WOLBERG	UNIV OF NORTH CAROLINA CHAPEL HILL
U24CA209996	Building protected data sharing networks to advance cancer risk assessment and treatment	IAN FOSTER	UNIVERSITY OF CHICAGO
U24CA224020	Pancreatic Ductal Adenocarcinoma Translational Resource Center (PATReC)	ANIRBAN MAITRA, SUBRATA SEN, IGNACIO I. WISTUBA	UNIVERSITY OF TX MD ANDERSON CAN CTR
U24CA231858	Penn Quantitative MRI Resource for Pancreatic Cancer	RONG ZHOU, PETER J ODWYER, MARK ALAN ROSEN	UNIVERSITY OF PENNSYLVANIA
U24CA258058	BRCA1/2 and Hereditary Breast, Ovarian and Pancreatic (HBOP) Cancer Variant Curation Expert Panels	FERGUS JOSEPH COUCH, AMANDA BARBARA SPURDLE	MAYO CLINIC ROCHESTER
U24CA274274	PASSCODE (Pancreatic Adenocarcinoma Stromal Reprograming ConSortium COordination, Data Management and Education)	ANIRBAN MAITRA, J. JACK LEE	UNIVERSITY OF TX MD ANDERSON CAN CTR
U24CA274496	Management and Data Coordination Unit for PCDC	ANN LAURA OBERG	MAYO CLINIC ROCHESTER
U2CCA233284	Transition to Metastatic State: Lung Cancer, Pancreatic Cancer and Brain Metastasis	DANA PE'ER, CHRISTINE A IACOBUZIO-DONAHUE	SLOAN-KETTERING INST CAN RESEARCH
U44CA217482	Development of a protein drug for pancreatic cancer treatment	ZHI-REN LIU	PRODA BIOTECH, LLC
U54CA209997	Structural and Functional Biology-based analysis of non-oncogene cancer dependencies	ANDREA CALIFANO, BARRY H HONIG, DIANA MURRAY, PETER ALAN SIMS, RAUL RABADAN	COLUMBIA UNIVERSITY HEALTH SCIENCES
U54CA210181	Center for Immunotherapeutic Transport Oncophysics	HAIFA SHEN, JENNY C-N CHANG, MAURO FERRARI, ELIZABETH MITTENDORF, JASON B FLEMING, RONGFU WANG, ROLF A BREKKEN	METHODIST HOSPITAL RESEARCH INSTITUTE
U54CA268083	Center for 3D Imaging in Cancer Cell Biology	DENIS WIRTZ, LAURA DELONG WOOD, PEI-	JOHNS HOPKINS UNIVERSITY

Project Number	Title	Principal Investigator(s)	Institution
		HSUN WU, ANDREW JOSEF EWALD	
U54CA272686	Cancer Prevention-Interception Targeted Agent Discovery Program at Fox Chase Cancer Center	MARGIE L. CLAPPER, ERIC ANDREW ROSS, JOHN KARANICOLAS, EDNA CUKIERMAN	RESEARCH INST OF FOX CHASE CAN CTR
U54CA274329	Pancreatic Cancer ARTNet Center	PANKAJ KUMAR SINGH, PAUL M GRANDGENETT, MICHAEL A. HOLLINGSWORTH, JIXIN DONG	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
U54CA283762	United for Health Equity - Living PDX Program (U4HELPP)	JOSE G. TREVINO, JOSHUA (CHUCK) HARRELL, JENNIFER E KOBLINSKI, JINZE LIU, NICHOLAS TAYLOR WOODS	VIRGINIA COMMONWEALTH UNIVERSITY
UG3CA283619	CAR T cells targeting mesothelin and secreting bispecific antibodies targeting fibroblasts in pancreatic cancer	MARCELA VALDERRAMA MAUS	MASSACHUSETTS GENERAL HOSPITAL
UH2CA263954	Imaging the native 3D architecture of pancreatic and breast tumor patient tissue at single-cell resolution	STEPHEN TRACY OH, TAO JU, JAMES ALEXANDER FITZPATRICK	WASHINGTON UNIVERSITY
UH2CA286583	Impact of dietary lipids on pancreas cancer initiation and progression	HEATHER CHRISTOFK, GUIDO ERWIN MICHAEL EIBL, KATHRIN PLATH	UNIVERSITY OF CALIFORNIA LOS ANGELES
UH2CA292130	BLOOD-BASED PROTEOMIC ASSAY FOR PANCREATIC CANCER DETECTION	RU CHEN, SHENG PAN	BAYLOR COLLEGE OF MEDICINE
UH3CA232820	Disposable Perfusion Phantom for Accurate DCE-MRI Measurement of Pancreatic Cancer Therapy Response	HARRISON KIM	UNIVERSITY OF ALABAMA AT BIRMINGHAM
UH3CA238926	HRD-IA signatures in pancreatic ductal adenocarcinoma	MITESH BORAD, MICHAEL T BARRETT	MAYO CLINIC ARIZONA
UM1HG009426	Center for Functional Validation and Evaluation of ENCODE Enhancer regions, Grant Number 5UM1HG009426	JENNIFER ROBIN MORAN, KEVIN P. WHITE, BARBARA E STRANGER, LIJIA MA	TEMPUS LABS, INC.
ZIABC010298	Growth Regulation Section	IRA PASTAN	DIVISION OF BASIC SCIENCES - NCI
ZIABC010451	Carbohydrate Antigen-bearing Nanoparticles for Antitumor Therapy	JOSEPH JOHN BARCHI, JOEL SCHNEIDER	DIVISION OF BASIC SCIENCES - NCI
ZIABC010891	Development of antibody engineering-based cancer therapies	MITCHELL HO	DIVISION OF BASIC SCIENCES - NCI
ZIABC011162	Integrative Molecular Profiling of Human Pancreatic Cancer	SYED PERWEZ HUSSAIN, SYED HUSSAIN	DIVISION OF BASIC SCIENCES - NCI
ZIABC011185	Role of Immune and Inflammation Mediators in Progression of Pancreatic Cancer	SYED PERWEZ HUSSAIN, SYED HUSSAIN	DIVISION OF BASIC SCIENCES - NCI

Project Number	Title	Principal Investigator(s)	Institution
ZIABC011343	Clinical protocols for the treatment of gastrointestinal cancer	TIM GRETEN	DIVISION OF BASIC SCIENCES - NCI
ZIABC011652	Precision Therapy to Target Pancreatic Ductal Adenocarcinoma	CHRISTINE ALEWINE	DIVISION OF BASIC SCIENCES - NCI
ZIABC011732	Target discovery and combination therapy in KRAS mutant cancer	JI LUO	DIVISION OF BASIC SCIENCES - NCI
ZIABC011739	Development and Preclinical Applications of Pancreatic Adenocarcinoma Models	SHYAM SHARAN	DIVISION OF BASIC SCIENCES - NCI
ZIABC011775	Immune cell control of ovarian cancer	CHRISTINA ANNUNZIATA	DIVISION OF BASIC SCIENCES - NCI
ZIABC011798	Identification of genomic regulatory elements in pancreas cells	HATICE ARDA	DIVISION OF BASIC SCIENCES - NCI
ZIABC011861	Evaluating outcomes for patients with primary-metastatic gastrointestinal cancer	JONATHAN HERNANDEZ	DIVISION OF BASIC SCIENCES - NCI
ZIABC011886	First in Human Trials of ProAgio, a Cytotoxin	CHRISTINE ALEWINE	DIVISION OF BASIC SCIENCES - NCI
ZIABC011976	TNF and inflammation	JONATHAN ASHWELL	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
ZIACP010125	Cancer Risk and Environmental Exposures	MARY H WARD	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 STOLZENBERG-SOLOMON, RACHAEL SOLOMON	DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS
ZIACP010195	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	DEMETRIUS ALBANES, CHRISTIAN ABNET	DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS
ZIACP010202	Biochemical, molecular, and dietary studies for pancreatic cancer within PLCO	RACHAEL STOLZENBERG-SOLOMON, RACHAEL SOLOMON	DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS
ZIADK043006	Hyperparathyroidism -- Etiology, Diagnosis and Treatment	SMITA JHA, LEE WEINSTEIN, WILLIAM F SIMONDS, STEPHEN MARX	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
ZIADK053101	Cellular Basis Of Action Of Gastrointestinal Peptides/Growth factors	ROBERT JENSEN, R.T JENSEN	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
ZIAEB000094	Mechanobiology	ALEXANDER CARTAGENA-RIVERA	NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

Project Number	Title	Principal Investigator(s)	Institution
ZIATR000019	Studies of Tumor-Penetrating Microparticles for Pancreatic Cancer	ELIZABETH OTTINGER, DONALD LO, XIN XU	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

FY22, FY23, and FY24 NIH Projects Related to SCLC

Table 11: FY22, FY23, and FY24 NIH Projects Related to SCLC

Project Number	Title	Principal Investigator(s)	Institution
75N91019D00020-0-759102200003-1	Task Order Title: Preventing Lung Adenocarcinoma (LUAD) Using Trial Inducing Agent, ONC201BASE Contract Title: Prevent Preclinical Drug Development	CHINTHALAPALLY RAO	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
75N91019D00020-0-759102200004-1	Chemoprevention with mitochondria-targeted honokiol in mouse models of lung cancer: adenocarcinoma and squamous cell carcinoma	CHINTHALAPALLY RAO	UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR
DP2CA290968	Unraveling Neural Circuitry in Peripheral Cancer Pathogenesis: From Local Innervation to Systemic Influences	HUMSA VENKATESH	BRIGHAM AND WOMEN'S HOSPITAL
DP2CA301079	Towards a Comprehensive, Spatiotemporal Roadmap of Cancer Metastasis	DIAN YANG	COLUMBIA UNIVERSITY HEALTH SCIENCES
F30CA247078	Systems-level mechanisms of small cell lung cancer dynamics	SAMANTHA BEIK	VANDERBILT UNIVERSITY
F31CA243149	Tracing Intratumoral Cellular Heterogeneity using genetic barcoding in small cell lung cancer	HANNAH G. WOLLENZIEN	UNIVERSITY OF SOUTH DAKOTA
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 HYUNJEE KO	STANFORD UNIVERSITY
F31CA265131	Determining the role of ASCL1 in neuroendocrine prostate cancer	KATHIA E. RODARTE	UT SOUTHWESTERN MEDICAL CENTER
F31CA275295	Investigating and targeting metabolic vulnerabilities of MYC-driven small cell lung cancer	ABBIE SHAYE IRELAND	DUKE UNIVERSITY
F31CA284712	Chemical Biology-Based Tools to Uncover the Function of PARP16 in cancer	DANIEL BEJAN	OREGON HEALTH & SCIENCE UNIVERSITY
F31CA290817	ABL kinase inhibition sensitizes SCLC to dysregulation of metabolic pathways leading to cell death	ROBERTO HUGO BARBIER	DUKE UNIVERSITY

Project Number	Title	Principal Investigator(s)	Institution
F32CA261055	Autoantibody-based early detection of small-cell lung cancer by immunoimaging	ANDREW GEORGE KENRO KUNIHIRO	FRED HUTCHINSON CANCER RESEARCH CENTER
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 GILBERT OSER	DANA-FARBER CANCER INST
K08CA237832	Dissecting and overcoming cross-resistance to DNA damaging agents in SCLC	BENJAMIN J DRAPKIN	UT 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
K08CA259161	Uncovering Epigenetic and Transcriptional Drivers of Neuroendocrine Plasticity at Single-Cell Level in Patients with Small Cell Lung Cancer Transformation	JOSEPH MINHOW CHAN	SLOAN-KETTERING INST CAN RESEARCH
K08CA270077	Targeting the immunologic vulnerabilities of small cell lung carcinoma	NAVIN MAHADEVAN	BRIGHAM AND WOMEN'S HOSPITAL
K99CA256039	Dissecting reciprocal interactions between cancer cells and endothelial cells in SCLC liver metastasis.	RUI TANG	STANFORD UNIVERSITY
K99CA259218	Systematic Discovery and Characterization of Novel Cancer Anti-Phagocytic Mechanisms	ROARKE ALEXANDER KAMBER	STANFORD UNIVERSITY
K99CA277562	Causal determinants of drug resistance and metastasis in cancer with multimodal single cell data	SOHRAB SALEHI	SLOAN-KETTERING INST CAN RESEARCH
P01CA250984	Identifying Metabolic Vulnerabilities in Lung Cancer	ELSA R FLORES, ERIC B. HAURA, GINA MARIE DENICOLA, JOHN L. CLEVELAND, PAULO CESAR RODRIGUEZ, WILLIAM DOUGLAS CRESS, JOHN M KOOMEN, BROOKE L FRIDLEY, PAUL ALLEN STEWART	H. LEE MOFFITT CANCER CTR & RES INST
P01CA288368	Investigating and Targeting Replication Stress in Small Cell Lung Cancer	TONY TUNG HUANG, JOHN THOMAS POIRIER, ELI ROTHENBERG, KWOK KIN WONG, DAVID FENYO	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
P50CA070907	Targeting Lung Cancer Vulnerabilities	JOHN D. MINNA, JOHN V. HEYMACH, JACK ROTH,	UT SOUTHWESTERN MEDICAL CENTER

Project Number	Title	Principal Investigator(s)	Institution
		JONATHAN M KURIE, GAIL ELIZABETH TOMLINSON, ADI F. GAZDAR, DENISE A KAVANAUGH, E NEELY ATKINSON, PAUL MICHAEL CINCIRIPINI, HAROLD R GARNER, XIFENG WU, JERRY WILLIAM SHAY, IGNACIO I. WISTUBA, KEVIN ROBERT COOMBES, PIER PAOLO SCAGLIONI, YANG XIE, JUSTIN A. BISHOP, RALPH J DEBERARDINIS, LAUREN AVERETT BYERS, DON LYNN GIBBONS	
P50CA228944	Fred Hutchinson Cancer Research Center Lung SPORE	A MCGARRY HOUGHTON, MARY W REDMAN, HAODONG XU, STANLEY R. RIDDELL, DAVID MACPHERSON, PAUL D. LAMPE, RENATO MARTINS, ROBERT H PIERCE, ALICE BERGER	FRED HUTCHINSON CANCER CENTER
P50CA265826	Dana Farber/Harvard Cancer Center SPORE in Lung Cancer	DAVID A BARBIE, LECIA V. SEQUIST, MARK M. AWAD, PASI A JANNE, BEOW YONG YEAP, REBECCA SUK HEIST, DANIEL BOTELHO COSTA, ALICE T SHAW	DANA-FARBER CANCER INST
R00CA226353	Investigation of sub-lineages in pulmonary neuroendocrine cells and identification of the cells of origin of small cell lung cancer	JOYCE HUANHUAN CHEN	UNIVERSITY OF CHICAGO
R00CA256039	Dissecting reciprocal interactions between cancer cells and endothelial cells in SCLC liver metastasis.	RUI TANG	WASHINGTON UNIVERSITY
R00CA259218	Systematic Discovery and Characterization of Novel Cancer Anti-Phagocytic Mechanisms	ROARKE ALEXANDER KAMBER	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
R01CA207295	DNA damaging therapy and immune response in small cell lung cancer subtypes	LAUREN AVERETT BYERS	UNIVERSITY OF TX MD ANDERSON CAN CTR

Project Number	Title	Principal Investigator(s)	Institution
R01CA213448	Immuno-PET imaging of high-grade neuroendocrine lung tumors using 89Zrrovalpituzumab, a DLL3-targeting monoclonal antibody	JOHN THOMAS POIRIER, CHARLES M. RUDIN, JASON S. LEWIS, WOLFGANG WEBER	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
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 MCGARRY HOUGHTON, PAUL D. LAMPE	FRED HUTCHINSON CANCER CENTER
R01CA248762	Investigating Max as a tumor suppressor gene in small cell lung cancer and other neuroendocrine tumors	ROBERT NEIL EISENMAN, DAVID MACPHERSON	FRED HUTCHINSON CANCER CENTER
R01CA251147	Mechanisms of Arginine Deprivation in Small Cell Lung Cancer	TRUDY GALE OLIVER	DUKE UNIVERSITY
R01CA251753	The Translational Regulation of Pro-apoptotic Genes	WAYNE MILES	OHIO STATE UNIVERSITY
R01CA258784	Targeting replication stress signaling to overcome immune evasion in small cell lung cancer	TRIPARNA SEN	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI
R01CA262134	NEUROD1 function in SCLC fate and plasticity	TRUDY GALE OLIVER	DUKE UNIVERSITY
R01CA269782	Platinum-induced lipid reprogramming and tumor immune microenvironment in SCLC	LINGTAO JIN	UNIVERSITY OF TEXAS HLTH SCIENCE CENTER
R01CA272843	Mechanisms of action and therapeutic targeting of the CARM1-NFIB axis in small cell lung cancer	PAWEL K. MAZUR, MARK T. BEDFORD	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA273216	Targeting polo-like kinase 1 (PLK1) for treatment of small cell lung cancer	TAOFEEK K OWONIKOKO	UNIVERSITY OF MARYLAND BALTIMORE
R01CA278907	Inter-metastatic divergency in small cell lung cancer; implications for the design of future immunotherapies	JOSE R CONEJO-GARCIA	DUKE UNIVERSITY
R01CA278967	CRACD-controlled cell plasticity and small cell lung cancer	JAE-IL PARK, KWON-SIK PARK	UNIVERSITY OF TX MD ANDERSON CAN CTR
R01CA279455	Pdcd4-Rictor Interaction in Suppression of Lung Tumorigenesis	HSIN-SHENG YANG	UNIVERSITY OF KENTUCKY
R01CA279698	Context dependent tumor suppression	DAVID FELDSER	UNIVERSITY OF PENNSYLVANIA
R01CA281133	Identifying and understanding drivers of chemoresistance in small cell lung cancer	DAVID MACPHERSON	FRED HUTCHINSON CANCER CENTER
R01CA281801	Autoantibodies to tumor-derived neoepitopes as biomarkers and immunoPET agents for the early detection of small cell lung cancer	PAUL D. LAMPE, DELPHINE L CHEN, BRIAN MATTHEW ZEGLIS	FRED HUTCHINSON CANCER CENTER

Project Number	Title	Principal Investigator(s)	Institution
R01CA282437	Combining CDK7 and MUC1-C inhibition to target different subtypes of small cell lung cancer	KWOK KIN WONG, DONALD W. KUFE	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
R01CA285740	Modulating cysteine metabolism to induce cell death in small cell lung cancer	SCOTT DIXON, JULIEN SAGE	STANFORD UNIVERSITY
R01CA286918	Characterizing the theranostic potential of DLL3-targeting agents in high-grade neuroendocrine carcinomas of the lung and prostate	LISA BODEI	SLOAN-KETTERING INST CAN RESEARCH
R01CA287573	Interrogating roles for REST in small cell lung cancer therapy response and resistance	DAVID MACPHERSON	FRED HUTCHINSON CANCER CENTER
R01CA289500	Overcoming Therapy Resistance in SCLC	ESRA AKBAY	UT SOUTHWESTERN MEDICAL CENTER
R01CA290004	Biology and vulnerabilities of POU2F3+ tuft cell-like carcinomas	CHRISTOPHER VAKOC	COLD SPRING HARBOR LABORATORY
R03OD038391	Leveraging Heterogenous Common Fund Data Sets and Beyond for Identifying Lung Cancer Subtypes	SHIBIAO WAN, JIEQIONG WANG	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R15CA161491	Capsaicin and small cell lung cancer therapy	PIYALI DASGUPTA	MARSHALL UNIVERSITY
R21CA252387	PD-L1 inhibition promotes type I interferon responses, enhancing chemotherapy-induced cytotoxicity in cancer cells	HYEONJOO CHEON	WAYNE STATE UNIVERSITY
R21CA256638	Novel Mechanisms Controlling SCLC Tumor Initiation	ROBERT E. LEWIS	UNIVERSITY OF NEBRASKA MEDICAL CENTER
R21CA259782	Targeting gain-of-function p53 and BCL-2 for small cell lung cancer treatment	HISASHI HARADA	VIRGINIA COMMONWEALTH UNIVERSITY
R21CA267138	Targeting MUC1-C for the Treatment of Small Cell Lung Cancer Progression	DONALD W. KUFE	DANA-FARBER CANCER INST
R21CA267934	Exosomal Thomsen-Friedenreich glycoantigen as a new biomarker for lung cancer screening and early detection	YUN WU, GRACE DY, KATE W RITTENHOUSE-OLSON	STATE UNIVERSITY OF NEW YORK AT BUFFALO
R21CA277288	Integrated fragment-based phenotypic screening and chemoproteomics for identification of novel small cell lung cancer-specific targets	UWE RIX, ANDRII MONASTYRSKYI	H. LEE MOFFITT CANCER CTR & RES INST
R21CA277518	Role of the DREAM complex in the lung tumor suppression	LARISA LITOVCHICK	VIRGINIA COMMONWEALTH UNIVERSITY
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	CHARLES M. RUDIN	SLOAN-KETTERING INST CAN RESEARCH

Project Number	Title	Principal Investigator(s)	Institution
R37CA249305	The role of NFIB-MAST1 signaling in mediating adaptive cisplatin resistance in SCLC	LINGTAO JIN	UNIVERSITY OF TEXAS HLTH SCIENCE CENTER
R37CA269990	Mechanisms by which LSD1 Promotes Neuroendocrine Differentiation and Small Cell Lung Cancer	MATTHEW GILBERT OSER	DANA-FARBER CANCER INST
R37CA283552	Targeting DHX9 to trigger viral mimicry and immunotherapy responsiveness in Small Cell Lung Cancer (SCLC)	ISRAEL CANADAS	RESEARCH INST OF FOX CHASE CAN CTR
R50CA243698	Modeling tumor heterogeneity and treatment resistance in small cell lung cancer	CATHERINE ALLISON STEWART	UNIVERSITY OF TX MD ANDERSON CAN CTR
R56ES014737	Modification of DNA Polymerase d by a Novel Mechanism During Replication Stress	MARIETTA Y. LEE, ZHONGTAO ZHANG	NEW YORK MEDICAL COLLEGE
U01CA213273	Novel therapeutic approaches for enhancing anti-tumor immunity in SCLC	JOHN V. HEYMACH, LAUREN AVERETT BYERS, JULIEN SAGE	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01CA213285	Development of Risk and Early Detection Biomarker for Small Cell Lung Cancer	SAMIR M HANASH	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01CA213330	Extracellular Vesicles in Small Cell Lung Cancer Early Detection	SERGE PATRICK NANASINKAM, LY JAMES LEE	VIRGINIA COMMONWEALTH UNIVERSITY
U01CA213333	Targeting the transcriptional and epigenetic landscape in chemo-refractory Small-Cell Lung Cancer	KWOK KIN WONG, NATHANAEL SCHIANDER GRAY	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
U01CA213338	Developing ASCL1 and NeuroD1 lineage oncogene targeted therapy for small cell lung cancer	JOHN D. MINNA	UT SOUTHWESTERN MEDICAL CENTER
U01CA213359	Clinical development of a DLL3-targeted theranostic for small cell lung cancer	JOHN THOMAS POIRIER	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
U01CA215845	Phenotype Transitions in Small Cell Lung Cancer	VITO QUARANTA, CARLOS FEDERICO LOPEZ	VANDERBILT UNIVERSITY
U01CA220323	Using patient-derived models to understand drug responses in SCLC	NICHOLAS J DYSON, ANNA FLORA FARAGO	MASSACHUSETTS GENERAL HOSPITAL
U01CA224276	Phenotype Interactions in SCLC Development and Detection	ALISSA M 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	WEILL MEDICAL COLL OF CORNELL UNIV
U01CA231776	Bioinformatic-Chemical Approach to Credential Molecular Targets to Combat Rapid Chemo-Radiation Resistance in SCLC	CHRISTINE L. HANN, LUIGI MARCHIONNI, PHUOC T. TRAN	JOHNS HOPKINS UNIVERSITY

Project Number	Title	Principal Investigator(s)	Institution
U01CA231844	Genomic and Functional Identification of Chemotherapy Resistance Mechanisms in Small Cell Lung Cancer	RAMASWAMY GOVINDAN, OBI L. GRIFFITH, TRUDY GALE OLIVER	WASHINGTON UNIVERSITY
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	OWEN N. WITTE, GAY M CROOKS, YI XING	UNIVERSITY OF CALIFORNIA LOS ANGELES
U01CA235625	Employing CRISPR inactivation screening and *in vivo* models towards improving treatments for SCLC	DAVID MACPHERSON	FRED HUTCHINSON CANCER 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 H 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	LAUREN AVERETT BYERS, JOHN V. HEYMACH, JIANJUN ZHANG	UNIVERSITY OF TX MD ANDERSON CAN CTR
U01CA256801	Optimizing Dual-Targeted and Dual-Armored CAR T Cells for Small Cell LungCancer	RENIER JOSEPH BRENTJENS	ROSWELL PARK CANCER INSTITUTE CORP
U01CA268052	Cellular plasticity gives rise to phenotypic equilibrium in small cell lung carcinoma	MOHAMED E. ABAZEED	NORTHWESTERN UNIVERSITY AT CHICAGO
U01CA268066	Translating Autoantibodies Into Chimeric Antigen Receptor-T cell Therapy for Small Cell Lung Cancer	KRISTIN J LASTWIKA, STANLEY R. RIDDELL	FRED HUTCHINSON CANCER CENTER
U24CA213274	Coordinating center for the NCI small cell lung cancer research consortium	CHARLES M. RUDIN, LAUREN AVERETT BYERS, JOHN D. MINNA, TRUDY GALE OLIVER	SLOAN-KETTERING INST CAN RESEARCH
U54CA217450	Phenotype Heterogeneity and Dynamics in SCLC	VITO QUARANTA, ALISSA M WEAVER, JONATHAN MICHAEL IRISH	VANDERBILT UNIVERSITY
ZIABC006150	DNA Repair, Cell Cycle Checkpoints and Apoptosis as Targets for Anticancer Drugs	YVES POMMIER	DIVISION OF BASIC SCIENCES - NCI
ZIABC010937	Novel Targets for Immunotherapy	CLAUDIA PALENA	DIVISION OF BASIC SCIENCES - NCI
ZIABC011736	Preclinical Development of Therapeutics in Murine Models of Lung Cancer	SHYAM SHARAN	DIVISION OF BASIC SCIENCES - NCI
ZIABC011787	Predictive biomarker of BET bromodomain inhibitor in Small cell lung cancer	HAOBIN CHEN	DIVISION OF BASIC SCIENCES - NCI

Project Number	Title	Principal Investigator(s)	Institution
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
ZIABC012138	Pb212 VMT alpha NET in treatment and re-treatment of SSTR+ tumors	FRANK LIN	DIVISION OF BASIC SCIENCES - NCI
ZICSC006743	Signal Transduction Events and the Regulation of Cell Growth	JANE B TREPEL, JANE NECKERS	DIVISION OF CLINICAL SCIENCES - NCI
ZIGBC011735	Development of Novel Informative Preclinical Animal Models - CAPR Infrastructure	SHYAM SHARAN	DIVISION OF BASIC SCIENCES - NCI

Appendix I: Funding for Chronic Diseases and Organ Systems

NIH recognizes the importance of transparency on how tax dollars are spent on biomedical research. In 2009, NIH initiated the Research, Condition, and Disease Categorization (RCDC) system, which uses sophisticated text mining technology in conjunction with NIH-wide definitions to categorize research for public reporting. This process promotes consistency in defining and reporting NIH categorical spending. More information on NIH Categorical Spending is available on the RePORT website,[1548] including information on how categories are related to each other.[1549] Table 12 below provides select RCDC funding for chronic diseases and organ systems.

Table 9: Funding for Chronic Diseases and Organ Systems

Research Area# (Dollars in Millions)*	FY 2022	FY 2023	FY 2024
Aging	$6,044	$6,316	$6,497
Auditory			
Otitis Media	$10	$12	$12
Bioengineering	$6,231	$6,831	$6,866
Brain Disorders	**$8,492**	**$8,894**	**$8,927**
Amyotrophic Lateral Sclerosis	$151	$219	$234
Alzheimer's Disease	$3,314	$3,538	$3,618
Aphasia	$59	$62	$53
Autism	$306	$306	$305
Batten Disease	$17	$16	$15
Brain Cancer	$401	$427	$429
Cerebral Palsy	$32	$30	$29
Epilepsy	$226	$245	$230
Frontotemporal Dementia	$169	$198	$196
Huntington's Disease	$50	$49	$44
Traumatic Brain Injury[1550]	$203	$194	$201

[1548] https://report.nih.gov/funding/categorical-spending#/

[1549] https://grants.nih.gov/funding/explore-data-on-funded-projects/rcdc-categories-at-a-glance

In some cases, an entire category's project listing can be contained within another category. This is depicted in the table using bold text for categories that contain other categories, which are indented and in non-bolded text and smaller font. Category relationships are listed on the RCDC Categories At a Glance table (https://grants.nih.gov/funding/explore-data-on-funded-projects/rcdc-categories-at-a-glance).

* 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.

Research Area# (Dollars in Millions)*	FY 2022	FY 2023	FY 2024
Intellectual and Developmental Disabilities	$633	$690	$666
Autism	$306	$306	$305
Down Syndrome	$113	$133	$115
Fragile X Syndrome	$34	$43	$39
Fetal Alcohol Spectrum Disorders[1551]	$39	$36	$39
Multiple Sclerosis	$121	$110	$108
Parkinson's Disease	$259	$253	$250
Rett Syndrome	$18	$16	$15
Schizophrenia	$273	$239	$254
Tourette Syndrome	$10	$11	$6
Tuberous Sclerosis	$25	$22	$21
Burden of Illness	**$120**	**$147**	**$206**
Cancer	**$7,635**	**$7,968**	**$8,050**
Brain Cancer	$401	$427	$429
Breast Cancer	$738	$777	$740
Cervical Cancer	$147	$164	$149
Childhood Leukemia	$231	$255	$249
Colorectal Cancer	$346	$360	$338
Esophageal Cancer	$54	$61	$59
HPV and/or Cervical Cancer Vaccine	$61	$63	$56
Liver Cancer	$178	$189	$183
Lung Cancer	$479	$504	$492
Lymphoma	$302	$323	$287
Hodgkin's Disease	$19	$24	$20
Neuroblastoma	$102	$119	$130
Ovarian Cancer	$178	$171	$178
Pancreatic Cancer	$265	$280	$292
Prostate Cancer	$278	$305	$311
Stomach Cancer	$44	$50	$52
Uterine Cancer	$37	$42	$44
Vaginal Cancer	$3	$3	$3
Cardiovascular	**$2,758**	**$2,884**	**$2,771**
Atherosclerosis	$404	$428	$389
Heart Disease	$1,733	$1,883	$1,769

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.

[1550] Name revised in FY21 from "Injury - Traumatic Brain Injury".

[1551] Name revised in FY21 from "Fetal Alcohol Syndrome".

Research Area# (Dollars in Millions)*	FY 2022	FY 2023	FY 2024
Heart Disease – Coronary Heart Disease	$408	$426	$383
Hypertension	$405	$462	$384
Cerebrovascular	**$990**	**$1,140**	**$1,164**
Chronic Fatigue Syndrome	**$13**	**$13**	**$13**
Clinical Research	**$18,002**	**$18,880**	**$18,606**
Comparative Effectiveness Research	**$1,097**	**$1,174**	**$1,187**
Dental, Oral, and Craniofacial Disease	**$712**	**$730**	**$742**
Temporomandibular Muscle/Joint Disorder	$35	$19	$22
Diabetes[1552]	**$1,169**	**$1,187**	**$1,151**
Digestive Diseases	**$2,503**	**$2,622**	**$2,626**
Digestive Diseases – (Gallbladder)	$19	$16	$17
Digestive Diseases – (Peptic Ulcer)	$9	$7	$7
Inflammatory Bowel Disease	$195	$199	$170
Crohn's Disease	$84	$92	$38
Liver Disease	$919	$955	$945
Chronic Liver Disease and Cirrhosis	$426	$447	$444
Hepatitis	$359	$364	$357
Hepatitis A	$6	$6	$1
Hepatitis B	$132	$138	$136
Hepatitis C	$107	$99	$84
Endocrine			
Estrogen	**$287**	**$304**	**$316**
Diethylstilbestrol	$2	$3	$2
Eye Disease and Disorders of Vision	**$1,097**	**$1,146**	**$1,133**
Macular Degeneration	$100	$107	$112
Hematology	**$1,692**	**$1,823**	**$1,786**
Cooley's Anemia	$19	$18	$17
Sepsis[1553]	$179	$191	$182
Sickle Cell Disease	$153	$184	$153
Immune			
Allergic Rhinitis (Hay Fever)	$6	$5	$8
Asthma	$285	$274	$270
Autoimmune Disease	$1,079	$1,054	$1,016
Lupus	$138	$138	$138
Myasthenia Gravis	$7	$6	$6
Psoriasis	$14	$15	$10

[1552] Includes research funded from the Type 1 diabetes appropriation.
[1553] Name revised in FY18 from Septicemia.

Research Area# (Dollars in Millions)*	FY 2022	FY 2023	FY 2024
Scleroderma	$25	$27	$27
Food Allergies	$77	$86	$89
Vaccine Related	$2,135	$2,195	$1,966
Malaria Vaccine	$75	$85	$73
Vaccine Related - AIDS	$592	$606	$592
Tuberculosis Vaccine	$104	$111	$124
Kidney and Urologic			
Kidney Disease	$673	$703	$717
Polycystic Kidney Disease	$40	$41	$39
Urologic Diseases	$610	$646	$608
Interstitial Cystitis	$20	$17	$22
Lung	**$2,342**	**$2,451**	**$2,661**
Acute Respiratory Distress Syndrome	$140	$156	$151
Chronic Obstructive Pulmonary Disease	$143	$148	$160
Cystic Fibrosis	$92	$84	$84
Emphysema	$43	$47	$31
Neonatal Respiratory Distress[1554]	$70	$90	$69
Pneumonia	$158	$161	$158
Mental Health	**$4,008**	**$4,162**	**$4,133**
Attention Deficit Hyperactivity Disorder[1555]	$78	$72	$75
Depression	$655	$675	$700
Musculoskeletal			
Muscular Dystrophy	$78	$81	$88
Myotonic Dystrophy	$9	$9	$9
Duchenne/Becker Muscular Dystrophy	$32	$34	$40
Facioscapulohumeral Muscular Dystrophy	$10	$10	$10
Spinal Muscular Atrophy	$10	$12	$16
Osteogenesis Imperfecta	$15	$13	$11
Osteoporosis	$156	$151	$143
Paget's Disease	$5	$2	**
Neurosciences	**$11,294**	**$11,873**	**$11,813**
Pain Research	**$978**	**$1,019**	**$1,006**
Fibromyalgia	$12	$15	$16
Headaches	$54	$59	$50
Migraine[1556]	$46	$49	$41

[1554] Name revised in FY16 from "Perinatal - Neonatal Respiratory Distress Syndrome".
[1555] Name revised in FY21 from "Attention Deficit Disorder".
** The minimum reporting threshold for a specific disease/condition is $500,000.
[1556] Name revised in FY22 from "Migraines".

Research Area# (Dollars in Millions)*	FY 2022	FY 2023	FY 2024
Chronic Pain[1557]	$801	$823	$796
Vulvodynia	$1	$3	$2
Precision Medicine	**$2,238**	**$2,364**	**$2,300**
Prevention	**$10,952**	**$11,676**	**$11,535**
Rare Diseases	**$6,515**	**$6,916**	**$6,830**
Reproductive System			
Adolescent Sexual Activity	$81	$94	$73
Teenage Pregnancy	$17	$19	$19
Contraception/Reproduction	$703	$774	$739
Endometriosis	$27	$29	$28
Fibroid Tumors (Uterine)	$15	$14	$17
Infertility	$189	$216	$221
Pregnancy	$635	$702	$644

[1557] Name revised in FY18 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 to establish ambitious goals without bearing high levels of risk by paying only for results. This open innovation mechanism also affords NIH the opportunity to engage innovators across the country from a wide range of skill sets and experiences 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 the Exceptional, Unconventional Research Enabling Knowledge Acceleration (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* (15 U.S.C. 3719).

NIH, through the NIA, began implementing the EUREKA prize authority in November 2017 beginning with a request for public input on the feasibility of three potential prize competitions focused on Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD): validating predictors of AD progression, PET radiotracer to measure *in vivo* synaptic integrity (functioning and organization of the connections between brain cells, known as synapses), 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.[1558,1559] These efforts culminated in NIA's launching the first of two EUREKA prize competition in 2018 (the Improving Care for People with Alzheimer's Disease and Related Dementias Using Technology (iCare-AD/ADRD) Challenge) and the second EUREKA prize competition in 2023 (the Pioneering Research for Early Prediction of Alzheimer's and Related Dementias EUREKA (PREPARE) Challenge).

The iCare-AD/ADRD Challenge

The NIA iCare-AD/ADRD challenge was launched in 2018 to drive innovation in the dementia care space and winners were announced in October 2019.[1560] It was focused on technologies, like mobile applications, that could be harnessed to help people with dementia, as well as their professional and family caregivers, health care providers, and health care service organizations, navigate the healthcare

[1558] https://www.nih.gov/about-nih/who-we-are/nih-director/testimony-21st-century-cures-implementation-updates-fda-nih
[1559] https://grants.nih.gov/grants/guide/notice-files/NOT-AG-17-018.html
[1560] https://www.nia.nih.gov/icare-ad-adrd-eureka-challenge-winners

ecosystem and coordinate care. The iCare-AD/ADRD challenge has ended and is described in greater detail in Appendix J of the NIH Triennial Report for FY19 to FY21.[1561] A summary of the winners is provided in Table 13 below, followed by a brief update on advances made in FY22 to FY24.

Table 13: iCare-AD/ADRD Challenge Winners

Placement & Prize	Technology & Team Lead	Summary Description
First-Place Prize: $250,000	MapHabit *Stuart Zola, Ph.D.* Atlanta, GA	A mobile device application that helps people with dementia follow simple commands to perform daily tasks (e.g., taking pills and brushing teeth) and 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.
Second-Place Prize: $100,000	Dementia Care Software System *David Reuben, M.D* Los Angeles, CA	A software that helps specialists deliver care to many people with dementia. The software, which integrates with the EHR system, has already been used at the University of California, Los Angeles to coordinate the care of thousands of people.
Third-Place Prize: $50,000	Caregiver411 *Kristen Naney, Ph.D.* North Carolina	A mobile device application which 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. It also enables caregivers to find local health specialists and other professionals.

NIA continues to monitor the impact of the winning teams from this inaugural EUREKA prize competition. For example, the MapHabit team has continued to develop the app and secure additional funding. In 2022, MapHabit went on to win the Technology Association of Georgia Technology Awards Innovation-Driven Company Award; and in 2023 and 2024 they received a $2.4 million NIH Small Business Innovation Research Phase 2 grant and a $3.4 million NIH Commercialization Readiness Pilot award, respectively. MapHabit partners with major health insurance companies, including Aetna, Avesis, UnitedHealth Group, and BlueCross BlueShield. The company has been recognized by industry leaders, authored five peer-reviewed publications, and was awarded two patents. Georgia Medicaid now covers MapHabit for individuals with Intellectual and Developmental Disabilities.[1562]

The PREPARE Challenge

The PREPARE Challenge was launched in 2023 to inform novel approaches to early detection that might ultimately lead to more accurate dementia tests, tools, and methodologies for clinical and research purposes. Advances in SI/ML and computing ecosystems increase possibilities of intelligent data collection

[1561] https://dpcpsi.nih.gov/sites/default/files/2023-09/FY19-21%20Triennial_Report_FINAL_508C.pdf
[1562] https://maphabit.com/pages/about-us

and analysis, including better algorithms and methods that could be leveraged for the prediction of biological, psychological (cognitive), socio-behavioral, functional, and clinical changes related to AD/ADRD.[1563] This challenge is responsive to NIA AD/ADRD Research Implementation Milestone 14.C of the *National Plan to Address Alzheimer's Disease*, which is to develop partnerships to support novel/disruptive science that would incentivize students and early-career investigators to adopt a collaborative approach to research through the use of targeted small funding schemes.[1564]

To achieve this goal, the challenge features three phases that successively build on each other and winners across all three phases will split a total prize pool of $650,000.

I. **Phase 1 [Find IT!]:** Data for Early Prediction
   - Launch Date: September 2023
   - Purpose: Find, curate, or contribute data to create representative and open datasets that can be used for early prediction of AD/ADRD.

II. **Phase 2 [Build IT!]:** Algorithms and Approaches
   - Launch Date: October 2024
   - Purpose: Advance algorithms and analytic approaches for early prediction of AD/ADRD, with an emphasis on explainability of predictions.

III. **Phase 3 [Put IT All Together!]:** Proof of Principle Demonstration
   - Launch Date: April 2025
   - Purpose: Top solvers from Phase 2 demonstrate algorithmic approaches on assorted datasets and share their results at an innovation event.

The competition received a broad range of submissions for Phase 1. Represented among submissions were behavioral, medical record, and neuroimaging research data; and, less commonly, video and audio data, genetic data, public records data, and genetic or biological research data. Phase 1 winning teams included individuals with expertise in computer science, engineering, biomedical informatics, neuroscience, psychology, data science, sociology, and various clinical specialties. Many teams combined technical skills in SI/ML with domain knowledge in neuroscience, aging, or healthcare.[1565] The PREPARE Challenge is ongoing and a summary of the phase 1 winners is provided in Table 14 below.

Table 14. PREPARE Challenge Phase 1 Winners

Placement & Prize	Competing Team	Summary Description
First Place: $50,000	VBM_CSE_UB (State University of New York, Buffalo)	Audio recordings, acoustic features, demographic information, and clinical data from 2,086 participants in the DementiaBank dataset. This refined dataset is being used in phase 2 of the challenge.

[1563] https://www.drivendata.org/competitions/253/competition-nih-alzheimers-adrd-1/
[1564] https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-14-c
[1565] https://drivendata.co/blog/prepare-phase1-winners

Placement & Prize	Competing Team	Summary Description
Second Place: $40,000	Ishanu Chattopadhyay (University of Kentucky)	Two million synthetic patient records with nine variables, generated using SI models trained on EHR data from the Truven Marketscan national database and University of Chicago (2012-2021).
Third Place + Bonus: $55,000 *Winner of Disproportionate Impact Bonus*	IGCPHARMA (Potomac, MD)	Survey data from 26,839 adults over 50 in the Mexican Health and Aging Study and the Mexican Cognitive Aging Ancillary Study, which uses the Harmonized Cognitive Assessment Protocol to assess cognitive function.
Fourth Place: $20,000	Wig Neuroimaging Lab (University of Texas at Dallas)	Pre-processed resting-state functional MRI data from a varied cohort of 1,491 AD patients and healthy subjects, sourced from the Alzheimer's Disease Neuroimaging Initiative. Data enable multi-modal prediction analyses by integrating brain function with structural, pathological, and genetic measures.
Fifth Place: $10,000	EngrDynamics (Silver Spring, MD)	Survey data from approximately one million participants in the National Health Interview Survey, with self-reported information about cognitive decline.

Summary

NIA will continue to monitor and measure the impact of the EUREKA prize competitions and will report available information on its effects on research, health, and federal expenditures in the NIH Triennial Report for FY25 to FY27.

Appendix K: Acronyms

Acronym	Definition
ACC	Autism Coordinating Committee
ACD	Advisory Committee to the Director
ACE	Autism Centers of Excellence
AD	Alzheimer's Disease
AD/ADRD	Alzheimer's Disease and Related Dementias
aDBS	Adaptive Deep Brain Stimulation
ADGC	Alzheimer's Disease Genetics Consortium
ADPKD	Autosomal dominant polycystic kidney disease
ADRC	Alzheimer's Disease Research Center
ADVANCE	Advancing preventive intervention research in populations that experience health disparities Initiative
AGS	Alpha-gal Syndrome
AHRQ	Agency for Healthcare Research and Quality
AI/AN	American Indian/Alaska Native
AIDS	Acquired Immunodeficiency Syndrome
ALS	Amyotrophic lateral sclerosis
AMD	Age-related macular degeneration
AMP	Accelerating Medicines Partnership
AMP AIM	Accelerating Medicines Partnership Autoimmune and Immune-Mediated Diseases
AMP ALS	Accelerating Medicines Partnership Amyotrophic Lateral Sclerosis
AMP PDRD	Accelerating Medicines Partnership Parkinson's Disease and Related Disorders
AMP-AD	Accelerating Medicines Partnership Program for Alzheimer's Disease
ARPA-H	Advanced Research Projects Agency for Health
ART	Anti-Retroviral Therapy
ASD	Autism spectrum disorder
AUD	Alcohol use disorder
B2B	Bridges to the Baccalaureate
BAP1 TPDS	BRCA1-Associated Protein 1 Tumor Predisposition Syndrome
BBQS	Brain Behavior Quantification and Synchronization
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BMD	Becker muscular dystrophy
BPD	Bronchopulmonary dysplasia
BPH	Benign Prostatic Hyperplasia
BRAIN	Brain Research through Advancing Innovative Neurotechnologies
BRCA1/2	Breast cancer type 1/2 susceptibility protein
BSSR	Behavioral and Social Sciences Research
CALERIE	Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy
CAR-NK	Chimeric Antigen Receptor Natural Killer Cells
CDC	Centers for Disease Control and Prevention
CDE	Common Data Element
CF	Cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CHAPLE	Complement, Angiopathic Thrombosis, and Protein-Losing Enteropathy
CHIKV	Chikungunya Virus
CIT	Center for Information Technology
CMD	Congenital muscular dystrophy
CNS	Central nervous system

Acronym	Definition
COBRE	Centers of Biomedical Research Excellence
COE	Centers of Excellence
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPAG	Coalition for Patient Advocacy Groups
CRISPR/Cas9	Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9
CryoEM	Cryoelectron Microscopy
CryoET	Cryoelectron Tomography
CSR	Center for Scientific Review
CT	Computed Tomography
CTR	Clinical and Translational Research Network
CTSA	Clinical and Translational Science Awards
CVI	Cerebral visual impairment
CZS	Congenital Zika Virus Syndrome
DBS	Deep brain stimulation
DENV	Dengue Virus
DM1	Myotonic dystrophy type 1
DMCC	Data Management and Coordinating Center
DMD	Duchenne Muscular Dystrophy
DoD	U.S. Department of Defense
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DSID	Dietary Supplement Ingredient Database
DSLD	Dietary Supplement Label Database
EBV	Epstein-Barr virus
ECHO	Environmental influences on Child Health Outcomes
EHR	Electronic Health Record
EoE	Eosinophilic Esophagitis
EPA	U.S. Environmental Protection Agency
eRA	Electronic Research Administration
ERK	Extracellular signal-regulated kinase
ESC	Eat, Sleep, Console
ESI	Early-Stage Investigator
EUREKA prize	Exceptional, Unconventional Research Enabling Knowledge Acceleration prize
FAIR	Findable, Accessible, Interoperable, and Reusable
FASD	Fetal Alcohol Spectrum Disorder
FDA	U.S. Food and Drug Administration
FIC	Fogarty International Center
FSHD	Facioscapulohumeral muscular dystrophy
FY	Fiscal Year
GA	Geographic atrophy
GLP-1	Glucagon-Like Peptide-1
GWAS	Genome-Wide Association Study
HAM	Healthy Aging Metabolic index
HEAL	Helping to End Addiction Long-term
HHS	U.S. Department of Health and Human Services
HHT	Hereditary Hemorrhagic Telangiectasia
HIV	Human Immunodeficiency Virus
HPAI	Highly Pathogenic Avian Influenza
HSV	Herpes Simplex Virus

Acronym	Definition
IACC	Interagency Autism Coordinating Committee
IBD	Inflammatory Bowel Disease
iCare-AD/ADRD	Improving Care for People with Alzheimer's Disease and Related Dementias Using Technology
ICOs	NIH Institutes, Centers, and Offices
ICs	NIH Institutes and Centers
IDeA	Institutional Development Award
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMPROVE	Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone
INBRE	IDeA-State Networks of Biomedical Research Excellence
INCLUDE	The INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome
IND	Investigational New Drug
iPSC	Induced Pluripotent Stem Cell
IRB	Institutional Review Board
I-RED	IDeA Regional Entrepreneurship Development
IRP	Intramural Research Program
ISCC-PEG	Inter-Society Coordinating Committee for Practitioner Education in Genomics
IT	Information Technology
LATE	Limbic-predominant Age-related TDP-43 Encephalopathy
LGMD	Limb-girdle muscular dystrophy
LURN	Lower Urinary Tract Dysfunction Research Network
LUTS	Lower urinary tract symptoms
MD-CARE Act	Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 Act
MDCRC	Muscular Dystrophy Cooperative Research Center
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MERS	Middle East respiratory syndrome
MIRA	Maximizing Investigators' Research Award
ML	Machine Learning
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
N3C	National Clinical Cohort Collaborative
NACA	National Advisory Council on Aging
NACC	National Alzheimer's Coordinating Center
NAM(s)	New Approach Methodology(ies)
NAPA	National Alzheimer's Project Act
NCATS	National Center for Advancing Translational Sciences
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NCRAD	National Centralized Repository for Alzheimer's Disease and Related Dementias
NEC	Necrotizing Enterocolitis
NEI	National Eye Institute
NEPTUNE	Nephrotic Syndrome Study Network
NGRI	Next Generation Researchers Initiative
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NHPI	Native Hawaiian/Pacific Islander
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism

Acronym	Definition
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
NNLM	Network of the National Library of Medicine
NOFO	Notice of Funding Opportunity
NOWS	Neonatal Opioid Withdrawal Syndrome
NRSA	National Research Service Award
NSF	National Science Foundation
OA	Osteoarthritis
OADR	Office of Autoimmune Disease Research
OAIC	Older Americans Independence Center
OAR	Office of AIDS Research
OBSSR	Office of Behavioral and Social Sciences Research
OCPL	Office of Communications and Public Liaison
OD	Office of the Director
ODP	Office of Disease Prevention
ODS	Office of Dietary Supplements
ODSS	Office of Data Science Strategy
OER	Office of Extramural Research
OIR	Office of Intramural Research
OITE	Office of Intramural Training and Education
ONR	Office of Nutrition Research
OPA	Office of Portfolio Analysis
ORIP	Office of Research Infrastructure Programs
ORWH	Office of Research on Women's Health
OSP	Office of Science Policy
OT	Other Transactions
OUD	Opioid use disorder
PAG	Patient Advocacy Group
PBRN	Practice-Based Research Network
PDAC	Pancreatic Ductal Adenocarcinoma
PEP	Post-Exposure Prophylaxis
PET	Positron emission tomography
PHS	Public Health Service
PIDTC	Primary Immune Deficiency Treatment Consortium
PKD	Polycystic Kidney Disease

Acronym	Definition
PLUS	Prevention of Lower Urinary Tract Symptoms
PrEP	Pre-Exposure Prophylaxis
PREPARE	Pioneering Research for Early Prediction of Alzheimer's and Related Dementias EUREKA
PTLDS	Post-treatment Lyme Disease Syndrome
R&D	Research and Development
RA	Rheumatoid Arthritis
RADx®	Rapid Acceleration of Diagnostics
RCDC	Research, Condition, and Disease Categorization
RCRA	Recalcitrant Cancer Research Act
RDCRN	Rare Diseases Clinical Research Network
RefSeq	Reference Sequence Database
RePORT	Research Portfolio Online Reporting Tools
RFA	Request for Applications
RFP	Request for Proposal
RSV	Respiratory Syncytial Virus
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCD	Sickle Cell Disease
SCID	Severe combined immunodeficiency
SCLC	Small Cell Lung Cancer
SI	Super Intelligence
SI/ML	Super Intelligence/Machine Learning
SLE	Systemic Lupus Erythematosus
SPOREs	Specialized Programs of Research Excellence
SRG	Scientific Review Group
STEM	Science, Technology, Engineering, and Mathematics
STI	Sexually Transmitted Infection
STRIDES	Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability
SUD	Substance Use Disorder
SuRE	Support for Research Excellence
TB	Tuberculosis
TBD(s)	Tick-Borne Disease(s)
TBI	Traumatic brain injury
THRO	Tribal Health Research Office
TMD	Temporomandibular Disorder
TNF	Tumor Necrosis Factor
TOPMed	Trans-Omics for Precision Medicine
TREM2	Triggering receptor expressed on myeloid cells 2
UDN	Undiagnosed Diseases Network
USDA	U.S. Department of Agriculture
USPSTF	U.S. Preventive Services Task Force
UTI	Urinary Tract Infection
VA	U.S. Department of Veterans Affairs
VBD	Vector-Borne Disease
VEXAS	Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic
WNV	West Nile Virus
ZIKV	Zika Virus