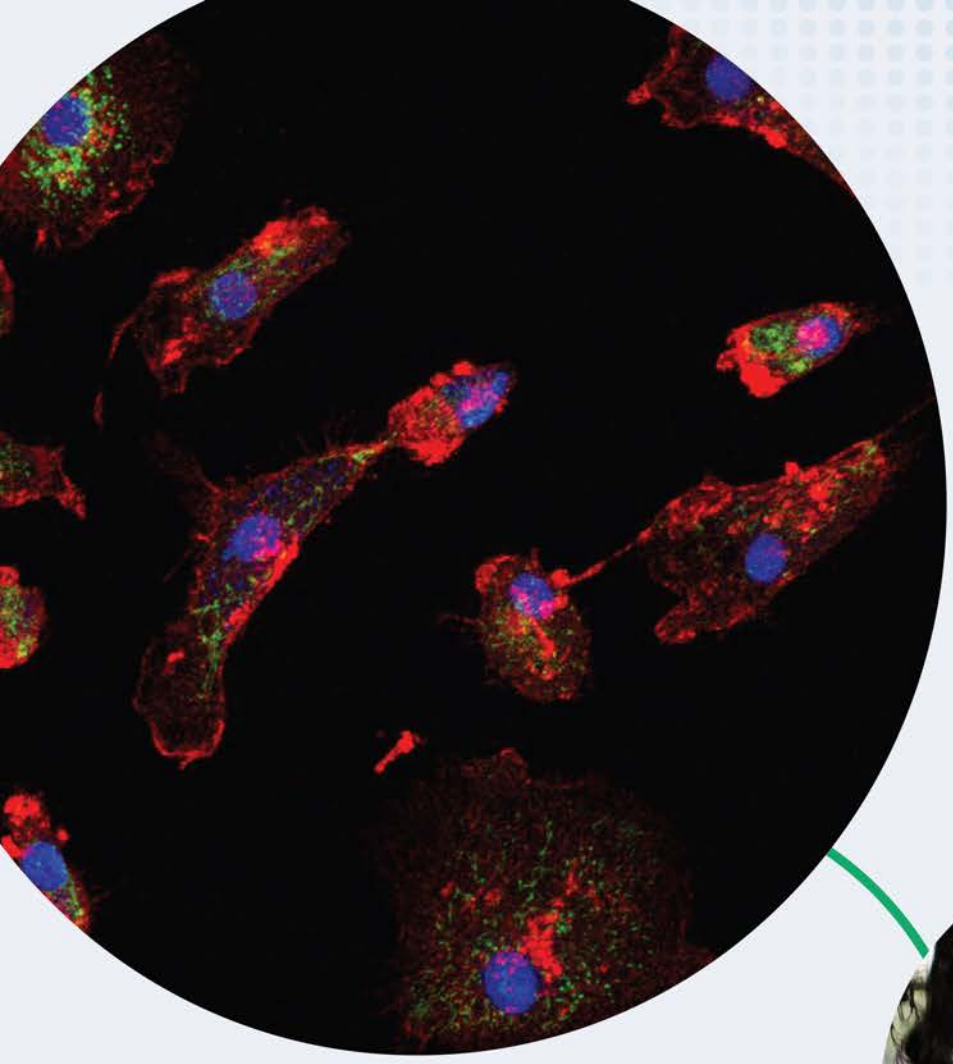
Report of the Director
National Institutes of Health

Fiscal Years 2012 & 2013

National Institutes of Health
Turning Discovery Into Health

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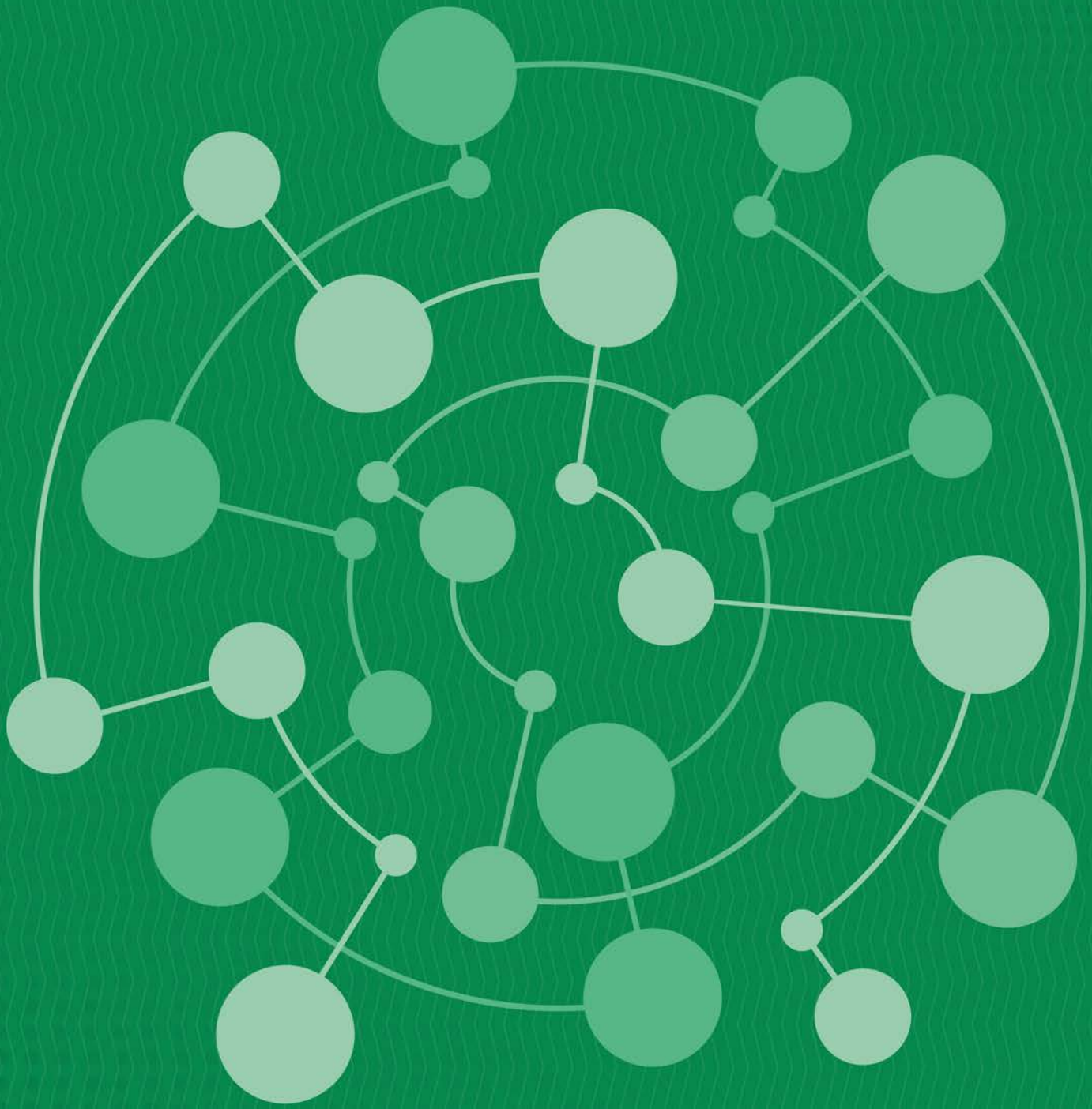

Preface

This is the fourth National Institutes of Health (NIH) Biennial Report, which is required by Section 403 of the Public Health Service (PHS) Act. Appendix A provides the language in the PHS Act that is relevant to this report. NIH's goal is for this report to serve as a useful reference for understanding NIH activities and operations, and the agency welcomes feedback on it.

Chapter Organization

Chapter 1 opens with a statement from the Director of NIH assessing the state of biomedical and behavioral research. It then describes NIH structure, policies, and procedures, focusing on the operations of the extramural and intramural research programs; mechanisms for strategic planning (including the activities and processes of the Division of Program Coordination, Planning, and Strategic Initiatives and its management of the Common Fund); and various cross-cutting activities not covered in the chapters that follow, such as programs that provide the platform for discovery, including training and career development activities and science literacy efforts.

Chapter 2 provides an overview of the NIH research portfolio. The chapter includes the following sections:

- Identifying Public Health Needs—Epidemiology
- Basic Research
- Preclinical Translational Research
- Clinical Research
- Postclinical Translational Research
- Information at the Service of Health
- Harnessing Technology

The chapter begins with a brief introduction describing the full continuum of biomedical research at NIH. The research continuum moves from basic research to preclinical translational research, clinical research, and finally postclinical translational research. In partnership with the other agencies of the U.S. Department of Health and Human Services (HHS), NIH aims to bring the rich evidence base of its research into clinical and community practice, ultimately turning discovery into health. The path in the continuum is not strictly linear, because all steps of biomedical research can inform and relate to other areas.

The introduction is followed by a summary of the NIH research portfolio relating to these research stages, across all of the Institutes and Centers (ICs) and Office of the Director (OD) program offices. The summary includes specific examples that illustrate how NIH research at each stage of the continuum augments human knowledge and improves public health. Chapter 2 also describes how NIH ensures the uptake of research results by clinical practitioners and the public. The chapter concludes with a description of NIH-funded research technologies, which provide innovative tools that are used within multiple steps in the continuum and often provide the means for exchange of information.

Chapter 3 addresses NIH research activities from the perspective of diseases, disorders, and adverse health conditions. The chapter includes the following sections:

- Cancer
- Neuroscience
- Life Stages, Human Development, and Rehabilitation
- Chronic Diseases and Organ Systems

- Autoimmune Diseases
- Infectious Diseases and Biodefense
- Public Health Emergency Preparedness
- Minority Health and Health Disparities

These topics, many of which are categories specified in the PHS Act (see Appendix A), are grouped together to address the intent of the statute by presenting information on diseases, disorders, and adverse health conditions in a standardized format. Each topic is addressed in a separate section.

Chapter 4 addresses NIH Centers of Excellence, which are diverse in focus, scope, and origin. The NIH Centers of Excellence described in this report are a subset: those established by statutory mandate. This chapter provides overviews, progress reports for Fiscal Years (FYs) 2012 and 2013 (covering programmatic and research activities and outcomes), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in the order of their establishment:

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

The appendices present reference documents and supporting data:

- Appendix A provides excerpts from the PHS Act that set the legal mandate for this Biennial Report and the inclusion of certain content within it.
- Appendix B contains excerpts of the *Report of the Advisory Committee on Research on Women's Health*.
- Appendix C provides the *Common Fund Strategic Planning Report, 2013*.
- Appendix D lists and provides links to the missions and strategic plans of the NIH ICs and the missions of the OD program offices.
- Appendix E consists of data on the primary NIH research training program, the National Research Service Award program, the National Library of Medicine training programs, and NIH graduate medical education activities.
- Appendix F contains excerpts of *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*.
- Appendix G provides catalogs of disease registries and other data systems.
- Appendix H provides information on actions undertaken to carry out scientific frameworks on recalcitrant cancer.
- Appendix I lists NIH funding levels for chronic diseases and organ systems.
- Appendix J contains a list of acronyms that are used in this Biennial Report.

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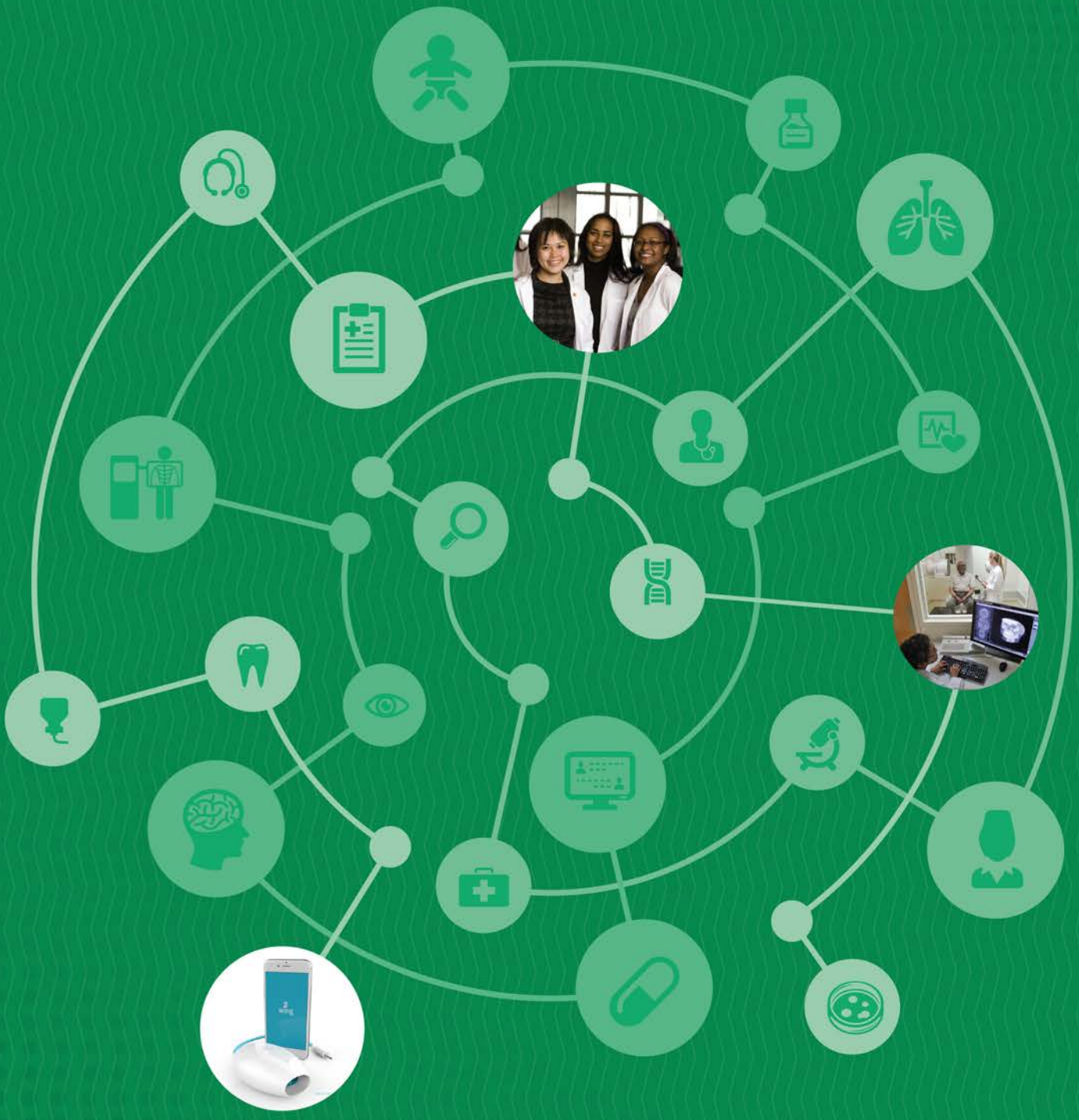


Chapter 1: About NIH

Statement of the Director

It is my honor to present to Congress the Biennial Report of the Director of NIH for FYs 2012 and 2013. With congressional support, NIH continues to discover fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to extend healthy life and reduce illness and disability. As the largest funder of biomedical research in the world, NIH has been the driving force behind decades of advances that have improved the health of people throughout the U.S. and across the globe.

Remarkable Contributions

For more than 125 years, NIH has been at the forefront of biomedical research, directing critical funding to research institutions throughout the nation and the world and stimulating lifesaving research breakthroughs. Begun as a one-room Laboratory of Hygiene in 1887, NIH has grown into a complex and multidisciplinary engine for discovery and innovation, comprising 27 ICs.

Research advances made by NIH have prompted a revolution in the diagnosis, treatment, and prevention of disease. Thanks to discoveries funded through NIH appropriations, NIH-supported research has met some of our nation's biggest health challenges. U.S. life expectancy has increased dramatically over the past century and continues to improve; between 1970 and 2010, the life expectancy of the average American increased by 7.9 years.[1] Babies born today have an average lifespan of more than 78 years, almost three decades longer than babies born in 1900.[2] The infant mortality rate in the U.S. has decreased from 26 per 1,000 births in 1960[3] to 6.1 per 1,000 births in 2010,[4] and the outlook for premature infants also has improved substantially.

In recent years, we have made impressive gains in the fight against many common diseases. For example, in the mid-20th century, cardiovascular disease caused nearly 40 percent of U.S. deaths, claiming the lives of many people still in their 50s and 60s.[5] Between 1968 and 2013, deaths due to coronary heart disease and stroke decreased by approximately 78 percent,[6] and these mortality rates continue to decline.[7] NIH-supported research led to minimally invasive techniques to prevent heart attacks and highly effective drugs to lower cholesterol, control high blood pressure, and break up artery-clogging blood clots. NIH-funded interventions also have motivated people to make lifestyle changes that promote health, such as eating less fat, exercising more, and quitting smoking. These and other factors have contributed to significant health improvements for Americans. Moreover, the percentage of all deaths attributed to heart disease and cancer, which accounted for 60 percent of all deaths at their peak in 1983, has dropped to 46 percent of deaths in 2013.[6]

In addition to reducing risk factors for cancer, groundbreaking NIH research led to the development of vaccines against cancer. Two Food and Drug Administration (FDA)–approved vaccines protect against cervical cancer caused by human papillomavirus (HPV). These two vaccines, Cervarix® and Gardasil®, prevent infection from HPV types 16 and 18, which cause about 70 percent of all cervical cancer. NIH research also has enabled advances in treatment of other kinds of cancer. For example, research

[1] CDC National Center for Health Statistics. *Health, United States, 2011: With Special Feature on Socioeconomic Status and Health.* Hyattsville, MD. 2012. http://www.cdc.gov/nchs/data/hus/hus11.pdf.
[2] Hoyert DL, et al. *Nat Vital Stat Rep.* 2012;61(6):1–51. PMID: 24984457.
[3] MacDorman MF, et al. *Vital Health Stat 20.* 1993;20(20):1–57. PMID: 25328980.
[4] MacDorman MF, et al. *Nat Vital Health Stat Rep.* 2014;63(5):1-6. PMID: 25252091.
[5] Fox CS, et al. *Circulation.* 2004;110(5):522–7. PMID: 15262842.
[6] Xu J, et al. *Natl Vital Stat Rep.* 2016;64(2):1-119. PMID: 26905861.
[7] Hoyert DL, et al. *Nat Vital Stat Rep.* 2012;61(6):1–51. PMID: 24984457.

on improving prostate cancer treatments, including radiation, chemotherapy, and hormonal therapy, has contributed to a significant decline in the death rate from this disease. Although prostate cancer remains the second leading cause of cancer-related deaths among men in the U.S., the death rate decreased from 38.4 to 21.9 deaths per 100,000 between 1990 and 2010.

One of NIH's greatest achievements over the past 30 years has been to lead the global research effort against the HIV/AIDS pandemic. Starting with basic research about how HIV works, discoveries all along the biomedical research continuum have led to the development of rapid HIV tests, a new class of HIV-fighting drugs, and, ultimately, lifesaving drug combinations. One study estimated that 14.4 million years of life have been gained among adults around the world since 1995 as a result of AIDS therapies developed through NIH-funded research.[8] In addition to contributing to progress on an HIV vaccine, NIH has led groundbreaking research on using HIV therapies to prevent new infections in people who are at high risk of infection.

An Economic Powerhouse

In accomplishing its mission, NIH promotes a healthier population, resulting in a healthier workforce and thus a stronger economy. NIH also directly effects the economy, having propelled research advances for the last 60 years by supporting a robust academic community that generates biomedical knowledge, patentable inventions, and trained scientists, including more than 140 NIH-funded Nobel laureates as of 2013. NIH funding supports research personnel at more than 2,500 institutions that are located in all 50 states, the U.S. territories, and more than 90 countries around the world.

Investing in NIH propels the U.S. economy by creating jobs and supporting scientific enterprises such as small biotechnology companies and scientific equipment sales. For example, a Battelle report indicated that the country's $12.3 billion investment in the Human Genome Project from 1988 to 2012 has resulted in nearly $1 trillion of economic growth—a 178-fold return on investment.[9] On a broader scale, a United for Medical Research report shows that in 2013, NIH supported 405,000 jobs across all 50 states, including jobs in almost every congressional district.[10] Every dollar invested by NIH gives back to our nation in multiple; for example, in 2012, NIH extramural funding generated an estimated $57.8 billion in new economic activity nationwide—nearly double taxpayers' investment.[11]

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

Unprecedented Opportunities: Neuroscience

Although NIH aims to facilitate scientific breakthroughs in all research areas, opportunities in neuroscience research generated focused investment in FY 2012 and 2013. Following the passage of the National Alzheimer's Project Act in 2011, HHS released the National Plan to Address Alzheimer's Disease in May 2012, and NIH hosted a research summit that same month to set forth a research agenda in keeping with the Plan's goals for effective prevention and treatment approaches. The recommendations focus on a spectrum of basic discovery and translational research activities that will help guide NIH investments in Alzheimer's disease research. Although NIH is still in the early stages of intensifying support in this area, capitalizing on recent advances in cognitive, clinical, behavioral, and molecular neuroscience research should propel the field at a rapid pace.

The brain is often described as the last big frontier in biomedical science, and as the technology used to study the brain evolves, the potential to make inroads in our

[8] Mahy M, et al. *Sex Transm Infect.* 2010;86(Suppl 2):ii48–55. PMID: 21106515.
[9] Batelle. *The Impact of Genomics on the U.S. Economy.* 2013. http://web.ornl.gov/sci/techresources/Human_Genome/publicat/2013BattelleReportImpact-of-Genomics-on-the-US-Economy.pdf.
[10] Kennedy JV, et al. *Healthy Funding: Ensuring a Predictable and Growing Budget for the National Institutes of Health.* United for Medical Research. 2015. http://www2.itif.org/2015-healthy-funding.pdf.
[11] Ehrlich E. *The Impact of a Sequester on the National Institutes of Health and Implications for Jobs and the U.S. Economy.* United for Medical Research. 2015. http://www.unitedformedicalresearch.com/wp-content/uploads/2013/02/UMR_Impact_of_Sequestration_2013.pdf.

understanding of this complex organ also advances. On April 2, 2013, President Obama launched the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, hailing it as "the next great American project." The BRAIN Initiative has been described as a bold project that can not only transform our fundamental understanding of the brain but also revolutionize our approach to brain diseases.[12] It is led jointly by NIH, the Defense Advanced Research Projects Agency (DARPA) of the U.S. Department of Defense (DoD), and the National Science Foundation (NSF). The National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS) are the lead ICs for the NIH BRAIN Initiative effort. Private organizations also are committed to ensuring success through investment in the initiative. As a result of this concerted effort, new technologies will emerge that will lead to a better understanding of the brain and ultimately may result in new treatments and even cures for devastating disorders and diseases of the brain and nervous system.

Unprecedented Opportunities: Translational Science

At the core of NIH's mission is basic research, and NIH-supported basic biomedical research has deciphered myriad physiological processes underlying health and disease. However, translating these basic discoveries into new and better treatments—long the purview of the private sector—has proved challenging. To meet this challenge, NIH established the National Center for Advancing Translational Sciences (NCATS) in FY 2012. NCATS' overall goal is to deliver more treatments to patients more efficiently. The process of developing a novel drug, device, or other intervention is a complex, costly, and risk-laden endeavor; less than 1 percent of compounds initially tested actually make it into patients' medicine cabinets. NCATS was established to address this problem by discovering new technologies and other approaches that could greatly accelerate the process of developing and deploying solutions that all translational researchers can use. NCATS is distinct in that it focuses not on specific diseases but on what is common among them and the scientific underpinnings of the translational science process.

[12] Insel TR, et al. *Science.* 2013;340(6133):687-8. PMID: 23661744.

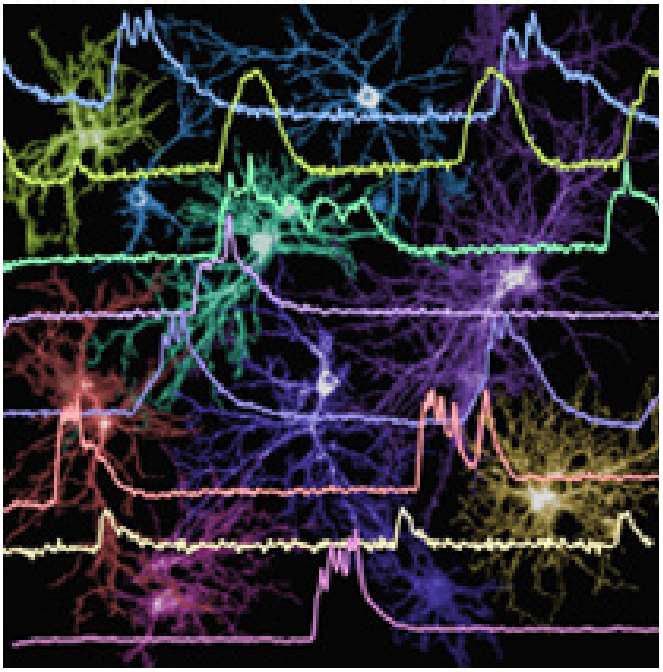


Figure 1-1. *Scientists funded by the NIH BRAIN Initiative will develop tools to watch the unique firing patterns of many neurons simultaneously in hopes of classifying them based on physical characteristics, such as size and shape, and functional characteristics, such as patterns of electrical activity.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

An early step in the translational science process is identifying molecular targets with therapeutic potential. Profound advances in genomics have yielded a multitude of potential targets, and new methods are needed to better predict effective, clinically relevant targets. The failure rate of drugs due to insufficient efficacy in Phase II trials—the first time a drug candidate is tested for efficacy in humans—is more than 50 percent.[13] To accelerate and streamline the process of validating potential drug targets, NIH is convening industry partners to develop infrastructure to share pre-competitive data and knowledge across sectors. Though still in early stages, these partnerships pose an unprecedented opportunity for increased sharing and collaboration that could increase the pace of drug discovery.

NIH is also engaged in other ways to speed the process of finding effective treatments for diseases. Among the first initiatives launched within NCATS is the Discovering New Therapeutic Uses for Existing Molecules program,[14] which focuses on repurposing drugs that have been abandoned in

[13] Arrowsmith J. *Nat Rev Drug Discov.* 2011;10(5):328–9. PMID: 21532551.
[14] http://www.ncats.nih.gov/ntu.

the development pipeline or approved to treat other diseases. The New Therapeutic Uses program matched biomedical researchers with a selection of pharmaceutical drug candidates to test ideas for new uses with the ultimate goal of identifying promising new treatments for patients. In June 2013, NIH made nine awards totaling $12.7 million, targeting diseases ranging from peripheral artery disease to muscular dystrophy to schizophrenia.[15] Although it is too early for complete results, three of the studies were treating patients within three months of the award, and one drug is showing promising results in treating aortic valve calcification.

Rising to New Challenges

The need for new approaches to prevention, diagnostics, and therapeutics is great. Despite the progress of the past century, our nation continues to face daunting public health challenges. Directly or indirectly, the chronic burdens placed on our health care system affect the health and well-being of all Americans. For example, Alzheimer's disease affects as many as 5.1 million people, and this number is expected to skyrocket as the baby boomer generation grows older. Obesity afflicts one-third of U.S. adults and 17 percent of children. And an estimated 9.6 million adults in the U.S. suffer from a seriously disabling mental illness, such as schizophrenia, bipolar disorder, or major depression.[16] In addition to these highly prevalent conditions, more than 6,800 rare diseases affect an estimated 25 to 30 million Americans. Facing the challenges presented by the number and complexity of diseases demands the innovative, scientifically based solutions that NIH research facilitates. Capitalizing on groundbreaking scientific achievements, unparalleled technological developments, and policies that continue to encourage scientists to collaborate and share data should catalyze the pace of discovery. Although many challenges lie ahead to improve health in this country, investing in NIH research offers hope to patients, families, and caregivers that a solution is within reach.

—Francis S. Collins, M.D., Ph.D.

[15] http://www.ncats.nih.gov/ntu/projects.
[16] Substance Abuse and Mental Health Services Administration (SAMHSA). *Results from the 2012 National Survey on Drug Use and Health: Mental Health Findings,* NSDUH Series H-47, HHS Publication No. (SMA) 13-4805 (2013).

NIH's Mission

NIH's mission is to seek 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 goals are:

- To foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health
- To develop, maintain, and renew scientific human and physical resources that will ensure the nation's capability to prevent disease
- To 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
- To exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science

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

- The causes, diagnosis, prevention, and cure of human diseases
- The processes of human growth and development
- The biological effects of environmental contaminants
- Mental, addictive, and physical disorders

It also directs programs for the collection, dissemination, and exchange of information in medicine and health, including the development and support of medical libraries and the training of medical librarians and other health information specialists.

Overview of NIH Structure and Organization

NIH is the primary federal agency for leading, conducting, and supporting biomedical and behavioral research. Composed of the OD and 27 ICs, NIH employs approximately 18,000 people and is the steward of an approximately $30 billion budget.[17] The leadership and financial support NIH provides to biomedical, behavioral, and social science researchers extends throughout our nation and the world.

Institutes and Centers

Each of the 27 NIH ICs has a focus on and expertise in a specific disease (e.g., cancer, diabetes), organ system (e.g., heart, eye), life stage (e.g., children, the aging population), overarching field of science (e.g., human genome, nursing, environmental health), or technology (e.g., biomedical imaging, bioengineering, information technology). The ICs *support* research and research training through extramural activities, and most also *conduct* research and research training through intramural activities.

Office of the Director

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

The NIH Office of Extramural Research (OER) provides the corporate framework for NIH administration of research grants and contracts, ensuring scientific integrity, public accountability, and effective stewardship of the NIH extramural research portfolio. Offices within OER include the Office of Administrative Operations; the Office of Data Analysis Tools and Systems; the Office of Extramural Programs; the Office of Laboratory Animal Welfare; the Office of Planning, Analysis, and Communication; the Office of Policy for Extramural Research Administration; and the Office of Research Information Systems.

The Office of Intramural Research (OIR) oversees and coordinates intramural research conducted within NIH laboratories and clinics. Offices within OIR include the Office of Animal Care and Use; the Office of Human Subjects Research Protections; the Office of Intramural Training and Education; the Office of NIH History and Stetten Museum; and the Office of Technology Transfer.

The role of the OD Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) is to identify emerging scientific opportunities, rising public health challenges, and scientific knowledge gaps that merit further research; assist NIH in effectively addressing identified areas; and develop and apply resources (databases, analytic tools, and methodologies) that will support priority setting and analyses of the NIH portfolio. The program offices within DPCPSI are the Office of Strategic Coordination, which manages the Common Fund; the Office of AIDS Research (OAR); the Office of Behavioral and Social Sciences Research (OBSSR); the Office of Disease Prevention (ODP); the Office of Research on Women's Health (ORWH);[18] and the Office of Research Infrastructure Programs (ORIP).[19] The Office of Dietary Supplements (ODS) and the Tobacco Regulatory Science Program are components of the ODP. The OD program offices fund research using IC award-making authorities. ICs often partner with one of these program offices to supplement their funding for a specific program or project. However, ORIP directly funds research through a separate award authority from those used by ICs.

The Common Fund was enacted into law by Congress through the 2006 NIH Reform Act to support cross-cutting, trans-NIH programs that require participation by two or more NIH ICs or would otherwise benefit from strategic planning and coordination. The requirements for the Common Fund encourage collaboration across the ICs while providing NIH with flexibility to determine priorities for Common Fund support. To date, the Common Fund has

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

[18] Appendix B contains excerpts of the *Report of the Advisory Committee on Research on Women's Health* for FYs 2011 and 2012, which provides a summary of the accomplishments of ORWH during this period, in addition to the website address for the full report.

[19] On December 23, 2011, President Barack Obama signed the Fiscal Year 2012 Omnibus Appropriations bill. As a result of this legislation, some of the National Center for Research Resources (NCRR) programs and the NIH Office of Science Education were transferred to the new Office of Research Infrastructure Programs, DPCPSI, OD, NIH.

been used to support a series of short-term, exceptionally high-impact, trans-NIH programs, including the High-Risk, High-Reward Research program, which supports several awards to test new ways of fostering innovation and also was authorized through the Reform Act.

Common Fund programs are intended to be:

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

Appendix C provides excerpts from the *Common Fund Strategic Planning Report* along with the website address where the full report may be found.

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

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

In addition, DPCPSI plans, supports, and provides technical assistance in the development of program evaluations and manages planning and reporting activities that support HHS's implementation of the Government Performance and Results Act (GPRA) and the GPRA Modernization Act, and other government-wide performance assessment activities.

ICs and OD Offices

The following is a list of NIH ICs and select OD program offices that advise the NIH Director, develop NIH policy, and provide essential NIH-wide oversight and coordination. The ICs and Offices are presented in the order in which they appear on the appropriations table in the Congressional Justification.[20] Appendix D provides brief descriptions of the missions of the ICs and OD program offices and links to their strategic plans. The mission statements and links to strategic plans provided in Appendix D classify and justify NIH priorities. Historical information about NIH, including information on the establishment of the categorical Institutes, Centers, and specialized offices, is maintained by the NIH Office of History, a component of OIR that preserves records of significant NIH achievements, innovative exhibits, and educational programs to enhance understanding of NIH biomedical and behavioral research.

Institutes and Centers:

- National Cancer Institute (NCI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of General Medical Sciences (NIGMS)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- National Eye Institute (NEI)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute on Aging (NIA)

[20] The NIH Congressional Justification ("CJ") provides the Senate and House Appropriations Committees detailed estimates and justifications for research and research support activities (infrastructure, administrative, etc.) that NIH would anticipate funding at the President's Budget Request level. More information available at https://officeofbudget.od.nih.gov/br.html.

- 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)
- National Center for Complementary and Alternative Medicine (NCCAM)[21]
- John E. Fogarty International Center (FIC)
- National Library of Medicine (NLM)
- NIH Clinical Center (CC)
- Center for Information Technology (CIT)
- Center for Scientific Review (CSR)

Office of the Director:

- Division of Program Coordination, Planning, and Strategic Initiatives
- Office of Extramural Research
- Office of Intramural Research
- Office of Management
- Office of Science Policy
- Office of Communications and Public Liaison
- Office of Equal Opportunity and Diversity Management
- Office of Legislative Policy and Analysis
- Office of Ombudsman/Center for Cooperative Resolution
- NIH Ethics Office
- Office of the Chief Information Officer

[21] On December 16, 2014, President Barack Obama signed the Consolidated and Further Continuing Appropriations Act of 2015, which changed the name of NCCAM to the National Center for Complementary and Integrative Health (NCCIH). The change was made to more accurately reflect the Center's research commitment to studying promising health approaches that are already in use by the American public. The mission of NCCIH remained unchanged. For historical accuracy, this report will refer to the IC as NCCAM.

Extramural and Intramural Research Programs

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

Extramural Research Program

More than $8 of every $10 appropriated to NIH is awarded by the ICs to the extramural biomedical and behavioral research community through grants and contracts. The extramural research community is composed of scientists, clinicians, and other research personnel affiliated with more than 2,500 organizations, including universities, medical schools, hospitals, and other research facilities located in all 50 states, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and other countries. In FY 2013, NIH funded the research of approximately 35,000 principal investigators through research grants, and the projects supported many thousands of additional personnel. With NIH support, these investigators and their research teams conduct the vast majority of research that leads to improvements in the prevention, detection, diagnosis, and treatment of disease and disability.

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

A key service OER provides for the NIH grants program is the electronic Research Administration (eRA) system. eRA supports the grant administration functions for grantees and federal staff from the submission of applications to the closeout of awards. eRA also provides services to other operating divisions of HHS, as well as other federal agencies, and supports more than 160,000 research personnel worldwide.

Grants Overview

NIH announces the availability of funds for grant programs by issuing Funding Opportunity Announcements (FOAs)[22] in the *NIH Guide for Grants and Contracts*[23] and on the *grants.gov* website. Most NIH grants funding is for projects that are investigator-initiated and submitted through omnibus parent announcements that span the breadth of the NIH mission. NIH uses program announcements (PAs), requests for applications (RFAs), and other types of FOAs to solicit applications for funding in targeted areas of research identified through strategic planning. Because many FOAs are trans-NIH opportunities, their preparation can involve considerable collaboration. In 2010, based on input from more than 1,000 stakeholders, OER implemented a shorter FOA format that eliminates redundancy, limits administrative detail, and directs applicants to the most up-to-date source of information.

The main types of grant funding that NIH provides are Research Grants (R series), Career Development Awards (K series), Research Training and Fellowships (T and F series), and Program Project/Center Grants (P series). Activity codes that incorporate the funding series differentiate the wide variety of research and research-related awards NIH makes. The most commonly used activity code is the R01, which designates a grant for a discrete, specified research project that is generally awarded for 3–5 years. Receiving a first R01 is a significant professional achievement for a scientist, traditionally marking attainment of scientific independence. Examples of other activity codes are:

- R41/R42 and R43/R44 for the Small Business Technology Transfer program and the Small Business Innovation Research program, respectively.
- R21 for exploratory/developmental research projects.
- R15 for Academic Research Enhancement Awards that support small-scale research projects at educational institutions that have not been major recipients of NIH research grants.
- R24 for resources that will enhance the capability of research projects.
- R25 for research education projects.

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

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

- F32 for postdoctoral individual fellowships under the National Research Service Award (NRSA).
- T32 for enabling institutions to make several NRSAs for both predoctoral and postdoctoral training.
- K08, a career development award, for providing support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience.
- P01 for research program projects that are broadly based, multidisciplinary, often long-term research and have a specific major objective or a basic theme.
- P30 for shared resources and facilities at research centers.

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

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

Contracts Overview

The Research and Development Contracts mechanism is another means by which NIH supports research and research-related activities. NIH typically uses research contracts to acquire goods or services for the direct benefit or use of the government. For example, contracts may be used to support research in areas of significant scientific interest, to further scientific knowledge, or to achieve a specific research goal. A research contract differs from a grant in a number of respects that are designed to comply with provisions of the Federal Acquisition Regulation. These differences include the manner used to solicit and negotiate the requirement, the level of NIH participation during contract performance, and the control of study results. Research contracts are awarded to universities, nonprofit organizations, and for-profit organizations. NIH announces contract opportunities in the *NIH Guide for Grants and Contracts*[24] and on the federal-wide *FedBizOpps.gov* website.[25]

[24] http://grants.nih.gov/grants/guide/description.htm.
[25] http://www.FedBizOpps.gov.

NIH Peer Review Process

All NIH grant, fellowship, and cooperative agreement applications and contract proposals for research and development funding undergo evaluation through peer review, in which external expert panels determine which applications or proposals are the most scientifically and technically meritorious (for grants, the first tier of peer review) and which are most programmatically relevant and should therefore be considered for funding (for grants, the second tier of peer review). The NIH peer review process is designed to be fair, equitable, timely, and free of bias. The two-tiered peer review system is mandated by statute (Section 492 of the Public Health Service Act) and by federal regulations governing "Scientific Peer Review of Research Grant Applications and Research and Development Contract Projects" (42 CFR Part 52h).[26]

The Center for Scientific Review (CSR) is the portal for receipt and referral of NIH grant applications and is the locus for the first level of review for most applications. Applications relevant to the NIH mission receive two 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 of scientific and technical merit. If the application is in response to an RFA, the SRG most often will be convened by the IC(s) responsible for the RFA. NIH uses established referral criteria to determine the appropriate SRG to carry out review and the IC(s) most suitable to potentially fund the project.

As noted above, the first level of review is conducted by SRGs that evaluate and give expert advice on the overall scientific and technical merit of the research proposed in the application, as well as the protection of human subjects, vertebrate animal welfare, and the budget and period of support requested. SRGs conducting the first level of review are composed primarily of nonfederal experts qualified by training or experience in particular scientific or technical fields, or authorities knowledgeable in the fields related to the applications under review. No more than one-fourth of

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

the members of any SRG may be federal employees. SRGs may include public members with perspective on the public health impact of the research being considered.

The second level of peer review is performed by the national advisory councils of the appropriate IC. National advisory councils are composed of scientific and public members chosen for their expertise, interest, or activity in matters related to a specific area of science, health, or disease. The vast majority of SRG-reviewed applications assigned to an IC go to the IC's Council,[27] which then recommends which applications should be considered for funding. Identifying applications that further specific program priorities and potential public health impact is a particularly important function of this second level of peer review. Advisory Councils recommend projects for funding but do not make funding decisions.

Funding Decisions

Applications that are scientifically meritorious, based on SRG review, and recommended by an IC's national advisory council are considered for funding. The score given to an application during the initial peer review process is important, but it is not the sole factor determining an IC's funding decision. Other considerations are portfolio balance, public health needs, programmatic relevance, IC priorities, requirements specified in congressional appropriations, and availability of funds.

Many ICs establish a "payline," which is a percentile-based[28] funding cutoff point that is determined at the beginning of the fiscal year by balancing the projected number of applications assigned to an IC with the amount of funds that NIH and the IC expect to be available for such projects. Applications that score within the payline are most likely to be funded. For applications that are not percentiled (e.g., applications reviewed by NIH ICs), ICs typically make awards up to the funding limit set aside for that particular funding opportunity. However, Advisory Councils consider, evaluate, and make recommendations on applications that score both within and outside the payline and funding limit.

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

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

Post-Award Administration

NIH policies extend into the post-award phase of research as well, so that NIH can monitor research progress and provide oversight. Scientific and administrative monitoring includes reviewing yearly progress and periodic financial reports submitted by grantees. NIH extramural staff monitor grants to identify potential problems and areas where technical assistance might be necessary. This active monitoring is accomplished through review of reports and correspondence from the grantee, audit reports, site visits, and other information available to NIH.[29,30,31] 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,

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

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

[29] http://grants.nih.gov/grants/funding/sbir_sttr_invention_letter.htm.

[30] http://grants.nih.gov/grants/guide/notice-files/not95-003.html.

[31] https://s-edison.info.nih.gov/iEdison/timeline.jsp.

the NIH Public Access Policy, and other matters. In addition, oversight of clinical research may involve data and safety monitoring and monitoring of inclusion of clinical research participants by sex/gender, race, and ethnicity.

Intramural Research Program

Approximately 11 percent of NIH funds support research and training activities carried out by NIH scientists in the NIH Intramural Research Program (IRP). The IRP aims to be a dynamic research environment for new generations of imaginative scientists to conduct fundamental research that reveals new principles of biology, provides new understandings of human disease, and changes treatment and prevention paradigms. The IRP research environment also is designed to attract and train a highly-talented and diverse cadre of scientists who will lead biomedical research in the 21st century.

The IRP laboratories are located on NIH campuses in the Bethesda, Rockville, Frederick, and Baltimore areas in Maryland; Research Triangle Park, North Carolina; Detroit, Michigan; Phoenix, Arizona; Framingham, Massachusetts; and the Rocky Mountain Laboratories in Hamilton, Montana. Approximately 1,100 principal investigators lead intramural research projects that involve more than 6,000 trainees ranging from high school students to postdoctoral and clinical fellows.

OIR is responsible for trans-NIH oversight and coordination of intramural research, human subject protections, animal welfare, training, policy development, laboratory safety, and technology transfer conducted within NIH laboratories and clinics. The Office is led by the NIH Deputy Director for Intramural Research, and the IRP in each IC is led by a Scientific Director who helps conduct oversight. The *Intramural Research Sourcebook* includes a summary of policies governing intramural research.[32]

The NIH IRP conducts basic, translational, and clinical research. Each IRP laboratory or clinic reports to its respective IC and is responsible for conducting original research consistent with the IC's goals. Most ICs have an IRP. As with the extramural program, intramural research proposals are generated by scientists. In the IRP, however, program directions and research priorities are not shaped primarily through grant awards[33] but rather through professional hiring and promotion decisions, external reviews, and 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, and tenured and tenure-track scientists undergo formal internal reviews annually. Resource allocations and promotions are determined based on these reviews. In addition, at least every four years, an external expert Board of Scientific Counselors reviews the work of each tenured/tenure-track scientist and makes recommendations regarding continuation or modification of projects and adjustment of resources (e.g., budget, space, and personnel). Moreover, IC Scientific Directors are evaluated by an external committee every 5 years, and each IC IRP is reviewed in its entirety by a "blue ribbon" panel approximately every 10 years. These panels assess and make recommendations concerning the impact of the research program, program balance, and other significant matters that play a role in the program's success.

Several offices manage research training for the IRP. The Office of Intramural Training and Education helps trainees in the program (including graduate students who are hosted by the IRP in partnership with universities in the U.S. and abroad) to develop scientific and professional skills needed to become leaders in the biomedical research community. The Office of Clinical Research Training and Medical Education covers all aspects of clinical training. In addition, most ICs have a Training Director who oversees their trainees.

NIH also provides primary administrative and research capacity for the National Toxicology Program (NTP), a federal interagency research program headquartered at NIEHS. NTP's goal is to safeguard the public by identifying which of the thousands of chemicals and other substances that humans are exposed to in the environment are toxic and may affect human health. Currently, NTP is studying endocrine disruptors, cell phone radiation, nanomaterials, dietary supplements, industrial chemicals, pharmaceuticals, and contaminants of drinking water to determine their

[32] http://sourcebook.od.nih.gov.

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

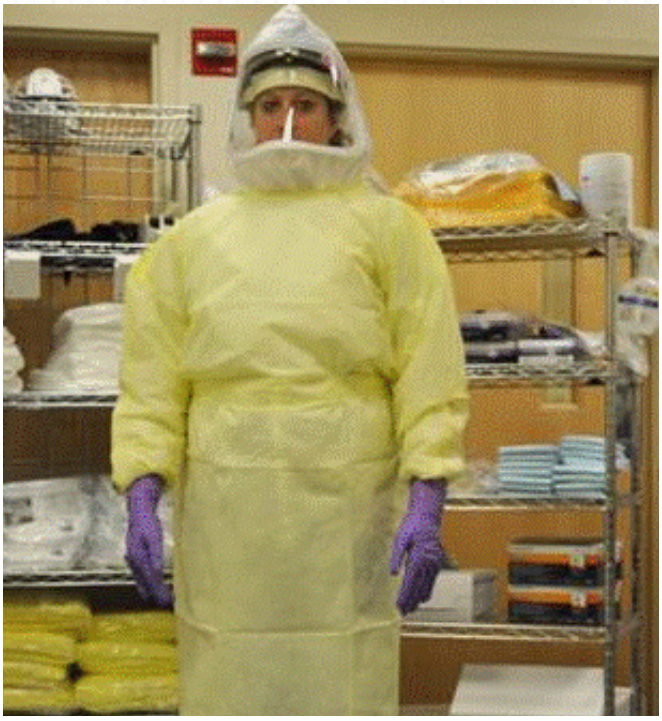


Figure 1-2. *The CC Special Clinical Studies Unit (SCSU) is an inpatient unit designed to facilitate the optimal performance of clinical research protocols involving frequent interventions. The unit's state-of-the-art infrastructure (isolation capabilities, staff training, and infection control algorithms) allows for the study of patients harboring potentially infectious pathogens or for the performance of clinical research protocols involving the use of potentially infectious vectors (e.g., attenuated live virus vaccine challenge studies). Pictured is an SCSU nurse wearing Personal Protective Equipment. Credit: SCSU.*

ability to cause cancer, damage genes, affect reproduction, and cause a variety of other health effects. The Program is developing approaches to advance high-throughput (high-speed and high-quantity) screening of chemicals, to reduce the number of animals used in research, and to apply systematic review methodology to literature-analysis activities to address questions in environmental health.[34]

NIH Clinical Center

The majority of NIH clinical research takes place at teaching hospitals around the country and overseas. However, at any given time, approximately 1,500 studies are in progress at the NIH Clinical Center (CC) in Bethesda, Maryland. The CC opened its doors in 1953, but the scope of NIH research expanded significantly with the opening of the Mark O. Hatfield Clinical Research Center in 2005.

The CC is the nation's largest hospital devoted entirely to clinical research. Each year, it serves more than 10,000 new patients and supports more than 50,000 inpatient days and 95,000 outpatient visits. In addition to approximately 1,200 credentialed physicians, dentists, and postdoctoral researchers, it houses more than 600 nurses and 450 other allied health professionals, including pharmacists, dieticians, medical and imaging technologists, therapists, and medical records and supply staff. Since the hospital opened, it has hosted nearly 500,000 clinical research participants. Because the CC is a research facility, only patients with the precise kinds or stages of illness under investigation are admitted for treatment. It 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.

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

[34] Birnbaum LS, et al. *Environ Health Perspect.* 2013;121(4):A108–9. PMID: 23548834.

Providing the Platform for Discovery

Research Training and Career Development

The biomedical and behavioral research that NIH conducts and supports—ranging from basic to applied—has long been recognized as critical to advancing the quality of health care in the nation and the world. As a result of NIH research, diseases such as AIDS, stroke, heart disease, and diabetes are being treated or prevented more successfully. Further research undoubtedly will lead to new or improved medical therapies for a spectrum of diseases and disorders. However, new advances in prevention, diagnosis, and treatment largely depend on the creativity, insight, and resources of the best scientists, and for these benefits to continue, there must be a regular source of highly trained, well-equipped, and innovative new investigators. Research training is where it all begins.

NIH research training and career development programs are designed to prepare new researchers to solve emerging problems in medicine and health. They aim to ensure that diverse pools of highly trained scientists are available in sufficient numbers and with appropriate expertise to generate new discoveries, take advantage of rapidly moving scientific developments, and bring science to bear on complex and evolving health care challenges. By sponsoring research training and career development programs in universities, teaching hospitals, NIH laboratories, and other research-intensive settings, NIH expects to ensure that trainees and newly trained investigators will not only be exposed to the latest research findings and techniques but also will be positioned to respond to developing national and international public health needs. NIH makes extra efforts to foster new investigators who focus on under-researched areas, such as clinical and translational research, rare diseases, health disparities, and global health issues.

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

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

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

Catalog of Research Training Activities

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

- Funded Ruth L. Kirschstein NRSA and NLM *Institutional* Research Training Grants, FYs 2011, 2012, and 2013
- Funded Kirschstein-NRSA *Individual* Fellowship Awards, FYs 2011, 2012, and 2013

Trans-NIH Programs and Initiatives

Training for a career in research typically requires a combination of specialized coursework and hands-on research experiences under the guidance of an established investigator. Most NIH-funded research training activities focus on predoctoral students and postdoctoral scholars. They are provided either through training grants (T awards), which are awarded to institutions to support a coordinated program of training for a group of students or scholars, or fellowships (F awards), which directly support an individual's training. The principal (in terms of size and breadth of coverage) NIH research training program for U.S. citizens and permanent residents is the Ruth L. Kirschstein NRSA program.[35] The program's goal is to support promising students and postdoctoral scholars with the potential to become productive, independent investigators in fields relevant to NIH's mission. Training activities can be in basic biomedical or clinical sciences, in behavioral or social sciences, in health services research, or in any other discipline relevant to the NIH mission, and they always include instruction in the responsible conduct of research. All ICs with funding authority award NRSA institutional research training grants, except FIC and NLM. Reflecting the unique nature of their missions, these two ICs have distinct training authorities, separate from the NRSA program.

Through the NIH-wide program of NRSA institutional training grants and fellowships, NIH ICs supported more than 16,500 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every state in FY 2013. Institutional training grants form the core of NIH's research training programs, providing support to more than 80 percent of all NRSA program participants. Training grants play a particularly important role at the predoctoral level: approximately 60 percent of trainees are graduate students, who are often engaged in coursework and laboratory rotations in preparation for identifying an area of research for in-depth study. See Appendix E for a breakdown of the demographics of NRSA participants and a summary of the number and type of doctoral degrees awarded to predoctoral NRSA recipients.

Individuals interested in research training in universities or departments that do not offer institutional training grants, as well as advanced students and postdoctoral scholars seeking tailored training opportunities, can apply directly to NIH for individual research training fellowships. NRSA fellowships provide recipients with valuable experience in initiating and testing their own research ideas before becoming full-fledged investigators.

Across NIH, NRSA training grants and fellowships help ensure the diversity of the research workforce by promoting research training opportunities for individuals from populations and backgrounds typically underrepresented in research. At the graduate and postdoctoral levels, NIH policy requires institutional training grant directors to take steps to recruit trainees from underrepresented groups, including racial and ethnic minorities and individuals with disabilities. Through the Ruth L. Kirschstein NRSA for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research,[36] NIH also provides graduate students from underrepresented groups with opportunities to pursue research training through individual fellowship awards. Because recruiting talented individuals into research training programs requires a pool of prepared applicants from which to draw, NIH offers undergraduate research training to honors students at selected institutions who are interested in a research career and who intend to pursue postgraduate education leading to a Ph.D., M.D./Ph.D., or other combined research degree.

The relative diversity of research training participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Among FY 2013 trainees and fellows who reported their race and ethnicity, 65.6 percent were white, 15.3 percent were Asian, 6.7 percent were African American, 10.2 percent were Hispanic, 0.4 percent were

[35] http://www.nigms.nih.gov/Training/IndivPredoc/Pages/default.aspx.

[36] http://grants1.nih.gov/grants/guide/pa-files/PA-11-112.html.

Native American, and 0.2 percent were Native Hawaiian or Pacific Islanders. More than 52 percent of trainees and fellows in FY 2013 were women.

NRSA training grants and fellowships may target broad-based or field-specific research training, depending on the needs identified by the administering IC. In recent years, this flexibility has allowed the NRSA program to accommodate interest in greater integration of training activities across NIH in order to fulfill workforce needs shared by multiple ICs.

Notable examples include the training grants and institutional career development awards in clinical and translational research that have been incorporated into the growing network of Clinical and Translational Science Awards (CTSAs)[37] administered by NCATS. Now active at more than 60 sites around the country, the CTSA program provides research training and career development opportunities in areas such as clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, behavioral science, and ethics to more than 750 NRSA trainees and new investigators annually. CTSA trainees are included in the NRSA data provided in Appendix E.

Additional trans-NIH training endeavors include the Big Data to Knowledge (BD2K) programs and the NIH Blueprint for Neuroscience Research. The BD2K initiative, launched in 2012, supports research, implementation, and training in data science and other relevant fields. NIH Blueprint for Neuroscience Research programs also are providing the next generation of scientists with extraordinary opportunities for training in integrated neuroscience. This cooperative effort between 15 ICs and Offices, under way since 2004, supports opportunities for research education for undergraduates and more advanced training programs in neuroimaging and computational neuroscience.

Career development opportunities also have been developed through interagency partnerships. Through the NIH-FDA Tobacco Regulatory Science Program, a series of career development award programs have been issued for junior investigators conducting tobacco regulatory research. This partnership marries the tobacco regulatory science expertise and resources of the FDA with the NIH biomedical, behavioral, and social sciences research expertise. Another trans-NIH initiative is the Early Independence Awards.[38] These awards, supported by the Common Fund, provide newly trained scientists who have the intellect, scientific creativity, drive, and maturity to flourish independently with a chance to forgo the traditional period of postdoctoral training after receiving their doctoral degree and pursue their own program of independent research. To date, Early Independence Awardees have lived up to their exceptionally high potential, publishing numerous high-impact papers, uncovering groundbreaking scientific insights, and earning recognition from the *Forbes* "30 Under 30" and the Presidential Early Career Awards for Scientists and Engineers.

NIH recognizes that traditional research-intensive positions are not the only means by which newly trained investigators can contribute meaningfully to the biomedical research enterprise. The Common Fund's Strengthening the Biomedical Research Workforce program[39] aims to enhance training opportunities for early-career scientists to prepare them for a variety of career options in biomedical research through a series of Broadening Experiences in Scientific Training (BEST) awards. Awardee institutions collaborate with nonacademic partners to ensure proven approaches can be disseminated broadly and adopted by the biomedical research training community.

As one component of a trans-NIH strategy to attract and retain talented individuals from all sectors of the population in biomedical research, the Common Fund launched the Enhancing the Diversity of the NIH-Funded Workforce program in FY 2013.[40] This program consists of three highly integrated initiatives: the Building Infrastructure Leading to Diversity (BUILD) initiative, which is a set of experimental training awards designed to learn how to attract students from diverse backgrounds into the training pipeline and to encourage their persistence in biomedical research careers; a National Research Mentoring Network, which is developing novel mentoring strategies, establishing standards and training for mentors, and developing a diverse network of mentors and mentees across the country; and the Coordination and Evaluation Center, which works across all initiatives and awardee institutions to determine what works and for whom and disseminates lessons learned to the broad biomedical research training community.

[37] http://www.ncats.nih.gov/ctsa.

[38] http://commonfund.nih.gov/earlyindependence.
[39] http://commonfund.nih.gov/workforce/index.
[40] http://commonfund.nih.gov/diversity/index.

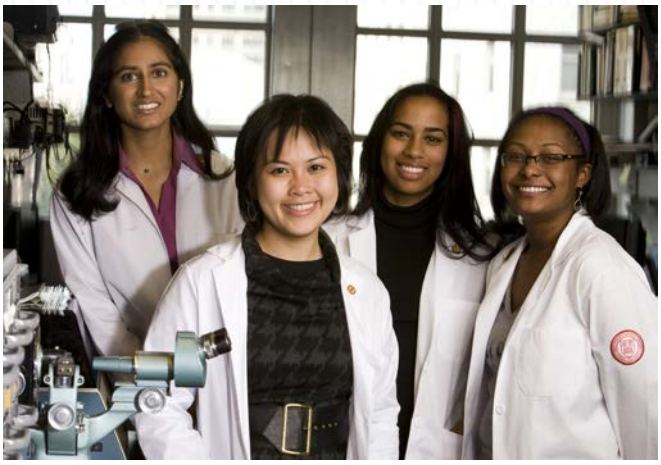


Figure 1-3. *Kirti Magudia, Marie Tran, Sharline Madera, and Nicole Ramsey of the Weill Cornell/Rockefeller/Sloan-Kettering Tri-Institutional MD-PhD Program. Credit: Topher Cox.*

In addition to its formal research training programs, NIH supports graduate and postdoctoral research experiences on research grants. Though this support is not an NIH "program" per se, its impact is significant. Graduate students and postdoctoral scholars acting as research assistants—often before or after a NRSA training grant appointment or fellowship—gain knowledge, skills, and experience that help prepare them for careers in research. To gain a better understanding of how graduate students and postdoctoral fellows contribute to research projects, in FY 2010, NIH asked investigators to identify all research project personnel on their annual progress reports. In 2013, NIH expanded that effort to collect information on the educational and demographic backgrounds of all students and postdoctorates working on NIH research projects.

The importance of networking, mentoring, and having good counsel for establishing a career as a scientist cannot be overstated, but these are especially important for women of color and other minorities. In 2012, NIH established the Women of Color Research Network, an online resource to connect women of color and others in the biomedical sciences with peers and potential mentors, assist them in navigating the NIH grants process, and help them find advice on their career development. The network has now grown to approximately 1,300 members.

IC Programs and Initiatives

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

To ensure a supply of investigators attuned to the challenges of both research and patient care, ICs also make awards for M.D./Ph.D. and other types of dual-degree training. The oldest and largest of these programs is the NIGMS Medical Scientist Training Program, which supports exceptional students pursuing an integrated program of graduate training in the biomedical sciences and clinical medicine. NIGMS also manages the Institutional Development Award (IDeA) program, which aims to ensure biomedical and behavioral research excellence throughout the U.S. by broadening the geographic distribution of NIH funding for biomedical research. The IDeA program fosters health-related research, enhances the competitiveness of researchers in states in which NIH support historically has been low, and serves specific populations such as rural and underserved communities in these states. The IDeA program strengthens the research capabilities of biomedical faculty and their institutions and provides promising undergraduate students with access to biomedical resources.

Reflecting the FIC mission to foster global health research and build research capacity in low- and middle-income countries, FIC institutional training grants (D43s) differ from those offered by the NRSA program or by NLM by allowing a broader range of participants and emphasizing the development of institutional partnerships and collaborations between U.S. and international universities and scientists. Most FIC research training programs target individuals from low- and middle-income nations, but several programs provide opportunities to U.S. students and postdoctoral fellows interested in global health research.

Figure 1-4. *Jessica Manning, M.D., conducted malaria vaccine research as a Fogarty International Clinical Research Scholar in Mali. Credit: Jessica Manning.*

Ultimately, the aim of FIC's research training programs is to strengthen sustainable research and collaborative research partnerships in the developing world.

FIC's programs build a research pipeline that is anchored to peer-reviewed research grants and designed to be collaborative, long-term, and flexible. For example, FIC's Global Health Program for Fellows and Scholars provides supportive mentorship, research opportunities, and a collaborative research environment for early-stage investigators from the U.S. and low- and middle-income countries to enhance their global health research expertise and their careers. FIC also offers training grants, such as the International Research Ethics Education and Curriculum Development Award, that not only enhance the career development of individuals from developing countries but also strengthen and sustain the capacity to support ethical clinical and public health research at home institutions.

NLM's research training portfolio generally parallels the structure and requirements of the NRSA program and reflects NLM's unique role as the primary federal sponsor of biomedical informatics research and training. NLM prepares the next generation of informatics researchers and health information specialists through institutional research training grants (T15s)[41] that support graduate and postdoctoral training in a broad range of topics, including health care informatics, translational bioinformatics, clinical research informatics, and public health informatics, as well as some specialized areas such as imaging and dental informatics. NLM also offers a fellowship on the NIH campus designed to attract physicians and others to NIH to pursue research in clinical informatics. Unlike NRSA research training awards, some NLM training programs are open to master's degree holders seeking further graduate-level coursework and hands-on training. In addition, NLM offers summer and year-round opportunities for students from high school through advanced graduate levels to collaborate with research staff on ongoing research and development projects in medical informatics and biomedical computation.

As outlined in the 2008 National Advisory Mental Health Council Workgroup on Research Training,[42] NIMH encourages the recruitment, training, and retention of outstanding physician-scientists from diverse backgrounds. To support advanced research experiences for outstanding early-career physicians and medical students from diverse backgrounds, NIMH launched an administrative supplement program. The purpose of this program is to improve the diversity of the mental health research workforce by supporting and recruiting early-stage investigators from groups that have been shown to be underrepresented in scientific disciplines relevant to mental health research on a national basis.[43]

Similarly, NIDDK has established a Network of Minority Health Research Investigators (NMRI)[44] to raise the number of minority researchers and to increase research on health disparities. The goal of NMRI is to foster a communication network of current and potential biomedical research investigators and technical personnel from traditionally underserved communities. This Network is led by the NIDDK's Office of Minority Health Research Coordination and has approximately 300 members.

[41] http://www.nlm.nih.gov/ep/GrantTrainInstitute.html.
[42] http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/investing-in-the-future_42525.pdf.
[43] http://grants.nih.gov/grants/guide/notice-files/NOT-MH-12-019.html.
[44] http://www.niddk.nih.gov/research-funding/process/diversity/network-minority-research-investigators/Pages/default.aspx.

Figure 1-5. *NIMHD's third Translational Health Disparities Course participants and staff. Credit: Ernie Branson, NIH.*

In 2013, NIMHD offered the third Translational Health Disparities Course: Integrating Principles of Science, Practice, and Policy in Health Disparities Research. The two-week intensive course, offered on a competitive basis to 80 individuals from the extramural community and from federal agencies, focused on integration of disciplines (including biological, social, behavioral, physical and environmental sciences, and law and economics) to understand science, practice, and policy issues in health disparities research.

Challenge competitions[45] can be a creative mechanism to support training and career development. NIBIB held annual Design by Biomedical Undergraduate Teams (DEBUT) Challenges in 2012 and 2013 for undergraduate students to develop innovative solutions to unmet health and clinical problems. Incentives such as these can serve as a launching pad for the next generation of innovators; past winners have gone on to create start-up biotechnology companies.

[45] Challenge and prize competitions are one path that federal agencies take to drive innovation and solve mission-centric problems. With a challenge competition, a "seeker" poses a problem or question to the public and "solvers" respond and submit solutions. An agency only awards those solutions that meet the criteria and are chosen as winners. More information available at https://www.challenge.gov/.

Figure 1-6. *The low-cost spirometer pictured here won the DEBUT Challenge in 2012 in the category of Technology to Aid Underserved Populations and Individuals with Disabilities. The spirometer addresses the lack of devices to measure lung function for the diagnosis and monitoring of respiratory diseases in the developing world, and it costs less than $10 (compare to $1,000–$2,000 for a traditional spirometer). Credit: Sparo Labs.*

Extramural Programs and Progress: Career Development

Given the ever-quickening pace at which science advances, investigators need opportunities to fully develop their scientific expertise and stay up to date. NIH career development awards (K awards)[46] address this need. Collectively, more than a dozen types of K awards support investigators as they establish their research careers, pursue new directions, or dedicate themselves to training and mentoring the next generation of scientists. Like the T and F training awards, some career development awards support institutional activities to nurture careers, and others directly support individual development.

Many career development awards are designed for researchers at specific career stages, particularly newly trained investigators. The NIH-wide Pathway to Independence Award[47] accelerates the transition from mentored to independent research by providing a bridging mechanism of an initial mentored period of one to two years followed by an independent phase, during which awardees establish their own research programs and apply for independent research support. Other "mentored" career development awards provide support for a sustained period of "protected time" for intensive research career development under the guidance of an experienced investigator. The expectation is that, with this experience, awardees will be able to take the final steps toward establishing independent research careers and becoming competitive for new research project grant funding. At the other end of the career spectrum, a number of ICs provide career development opportunities to mid-career and established investigators. These awards provide salary support for outstanding senior scientists and recognized leaders so that they can focus intensively on their research and mentor new investigators.

NIH Training and Career Development Program Evaluations and Assessments

Since the NRSA program was established in 1974, NIH training programs have been reviewed and evaluated regularly. The National Academy of Sciences (NAS) has undertaken regular reviews of the medical research workforce and recommended modifications in the size and focus of the NRSA program. In addition, NRSA program processes and outcomes are assessed regularly through recurring program evaluations, and performance is evaluated annually using GPRA measures. OER, which oversees the NRSA program, coordinates these reviews.

NAS Reviews

Over the past 30 years, the NRSA program has been the subject of more than a dozen studies by NAS, which has provided expert guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. In recent years, NIH has followed recommendations from NAS committees for enhancing stipend levels, promoting the early completion of research training, and improving workforce data collection and analysis.

[46] http://grants.nih.gov/training/careerdevelopmentawards.htm.
[47] http://grants1.nih.gov/grants/guide/pa-files/PA-11-197.html.

Evaluation of NIH Training and Career Development Programs

Evaluations of the outcomes of NRSA research training routinely have found that graduate students participating in NRSA programs complete their degrees in a shorter timeframe, are more likely to pursue research careers, and have greater subsequent success in research compared with students not participating in NRSA programs.[48] Similarly, assessments of NRSA postdoctoral training have found that NRSA postdoctoral fellows are more likely to successfully pursue research careers. A 2013 analysis found that 30 percent of former NRSA postdoctoral fellows received major NIH research grant funding within 10 years of their fellowship training, whereas 15 percent of other postdoctoral fellows did so.

Most recently, NIH evaluated the effects of its three most widely used types of mentored career development awards: K01, K08, and K23. Comparing similar groups of funded and unfunded applicants, NIH found that those who received a career development award were more likely to remain in research; publish their research findings; apply for and receive major NIH research grants; and, for those whose careers were tracked for sufficient time, apply for and receive a grant renewal.[49] Although all investigators receiving these career development awards fared well, having a mentored career development experience had the greatest impact on M.D.s and M.D./Ph.D.s.

Government Performance and Results Act (GPRA) Measures

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

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

IC Training Evaluations

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

Coordination and Oversight by the NIH Office of Extramural Research

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

Beginning in 2013, OER led the implementation of a series of recommendations from the NIH Advisory Committee to the Director Working Group on the Biomedical Research Workforce to enhance NIH training programs through modifications to existing training programs.[50,51] These changes included:

- Allowing graduate students in all health research–related fields an opportunity to compete for NIH graduate fellowships (F30 and F31) by extending these programs to all NIH ICs.
- Permitting more postdoctorates to transition to faculty positions more quickly by increasing NIH's overall support for the K99/R00 Pathway to Independence program and refocusing the eligibility period toward earlier-stage investigators.
- Enhancing career planning and mentoring by promoting the use of Individual Development Plans (IDPs) for all NIH-supported graduate students and postdoctorates.

[50] http://biomedicalresearchworkforce.nih.gov/docs/Biomedical_research_wgreport.pdf.
[51] http://biomedicalresearchworkforce.nih.gov/improve.htm.

- Updating existing electronic systems and initiating the development of new electronic systems to improve the accuracy and breadth of data on training and career outcomes.
- Leading the activities of the NIH Advisory Committee to the Director Physician-Scientist Workforce Working Group.

Intramural Activities

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

Among the intramural program's offerings are summer internships for high school, college, and graduate students. Recent college graduates who plan to apply to graduate or professional school also can spend a year engaged in biomedical research working side by side with NIH scientists. Current graduate students can spend a summer or a year as fellows engaged in biomedical research at NIH. The Graduate Partnerships Program[52] enables students to pursue research toward their degrees at NIH in partnership with a participating academic institution. By linking academic environments with the breadth and depth of research at NIH, the Graduate Partnerships Program offers a unique graduate experience. Similarly, the Medical Research Scholars Program[53] provides research-oriented medical, dental, and veterinary students an opportunity to engage in a mentored clinical or translational research project on the NIH campus. The NIDCR Office of the Clinical Director oversees the Dental Clinical Research Fellows Program, designed to provide training in the latest clinical, translational, and basic research methodologies related to dentistry and oral health.

Figure 1-7. *NIDCR IRP staff generate 3-D images to understand facial development and diagnose and treat craniofacial disorders using cone beam computed tomography. Credit: NIDCR.*

Training opportunities continue when scholars gain their graduate degrees. Year-round, NIH intramural laboratories employ fellows from the U.S. and abroad, creating a thriving, multidisciplinary intramural research community. The Postdoctoral Intramural Research Training Award[54] allows recent doctoral degree recipients who are U.S. citizens or permanent residents to enhance their research skills in the NIH intramural environment. Trainees pursue both basic and clinical research. A parallel program, Visiting Fellowships, serves foreign national doctoral-level scientists. NIGMS sponsors the Postdoctoral Research Associate program, which provides laboratory experience and intense mentoring to a selected group of fellows in the IRP. For clinicians, NIH offers opportunities for residency and subspecialty training, including graduate medical education accredited programs. (For program completion data, see Appendix E.) These graduate medical education programs enable research-oriented clinicians to weave research experience and training into their post–medical school training.

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

[52] https://www.training.nih.gov/programs/gpp.
[53] http://www.cc.nih.gov/training/mrsp/index.html.
[54] https://www.training.nih.gov/programs/postdoc_irp.

community—benefit from access to a wealth of NIH courses, seminars, and science career resources, providing information on both traditional and nontraditional science careers.

NIH Loan Repayment Programs

The NIH Loan Repayment Programs[55] are a vital component of our nation's efforts to attract eligible doctoral-level professionals to research careers in fields of special importance, including clinical, pediatric, health disparities, contraception and infertility, and AIDS research. To encourage qualified scientists to pursue research in these critical areas, the Loan Repayment Programs provide financial assistance for educational debt in exchange for a one-to-three-year research commitment, depending on the program. More than 1,300 program participants each year receive up to $35,000 annually in loan repayment and fulfill their commitments by conducting research in nonprofit, university, or government settings.

Science Education and Literacy

To remain a world leader in biomedical research, the U.S. must encourage and support students' curiosity and interest in science throughout their education. NIH funds a number of science education and literacy activities for students in elementary school through college. These programs support curriculum development, mentoring, outreach, and research experiences designed to recruit individuals with specific backgrounds to research careers or to increase the diversity of the biomedical workforce.

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

Curriculum supplements—ready-to-use, interactive teaching units—are one of NIH's science education efforts. Crafted through a unique collaboration of NIH scientists, teachers, and expert curriculum developers, the supplements are aligned with state education standards and are consistent with the National Science Education Standards. NIH has shipped more than 470,000 curriculum supplements upon request to K–12 educators across the nation. Topics covered include "Cell Biology and Cancer," "The Brain: Understanding Neurobiology Through the Study of Addiction," "Exploring Bioethics," and "Evolution and Medicine" for high school biology classes and "The Science of Healthy Behavior" and "Rare Diseases and Scientific Inquiry" for middle schools.[56]

NIH provides other types of school resources as well. *Findings* is a semiannual magazine targeted to high school and early college students that describes the excitement of cutting-edge research, the interesting people who pursue science careers, and the enjoyment they get from this work.[57] A companion website offers videos, podcasts, and interactive games expanding on the printed material. NIH also offers topical publications and school resources, such as slide kits, online quizzes, and science puzzles, that are used by teachers across the country to augment textbooks and enrich the classroom experience. Subject areas include cell biology, genetics, structural biology, chemistry, pharmacology, and computational biology. Classroom posters linked to selected publications also promote interest in science and research careers and are tremendously popular.

The NIH Blueprint for Neuroscience Research, a cooperative effort among 16 NIH ICs and Offices that support neuroscience research, supports a K–12 Science Education Award. NIH Blueprint funded eight science education grants that seek to improve and enhance neuroscience education in grades K–12 and to inspire future generations of neuroscientists. The grants focus on providing innovative neuroscience education to children throughout the U.S. using a variety of mechanisms, such as interactive teaching modules that can be accessed on iOS devices (e.g., the iPad), innovative Web-based games for classroom use, museum exhibits that include interactive components, and classroom activities.

[55] http://www.lrp.nih.gov/index.aspx.

[56] These curriculum supplements are free to teachers and may be ordered at http://science.education.nih.gov/supplements.

[57] http://publications.nigms.nih.gov/findings.

Figure 1-8. *Screenshot of the GeneEd homepage. Credit: NLM.*

NIH's Science Education Partnership Award (SEPA) program enables researchers, educators, and community groups to share their knowledge, expertise, and enthusiasm about health and science research with pre-kindergarten to grade 12 (P–12) students, teachers, and the general public. SEPA-funded classroom- and museum-based projects generate resources, including hands-on and problem-based curricula, interactive health exhibits, films, after-school and summer student internships, and professional development opportunities for teachers. The SEPA website is maintained by the SEPA community and provides universal access to educational resources, teacher training, health-based museum exhibits, and evaluation models that are developed through these SEPA-funded projects.[58]

Individual ICs provide other science education resources. For example, NLM and NHGRI have developed GeneEd, a Web-based education resource designed to increase genetic and genomic literacy. It provides access to genetics research, study guides, lesson plans, experiments, and activities for teachers and students in grades 6–12.[59] NLM also provides lesson plans for grades 3–12 that incorporate unique historical materials from the library and from its varied scientific databases, covering topics such as Civil War medicine, preventing the spread of infectious disease, forensic medicine, and environmental science.[60]

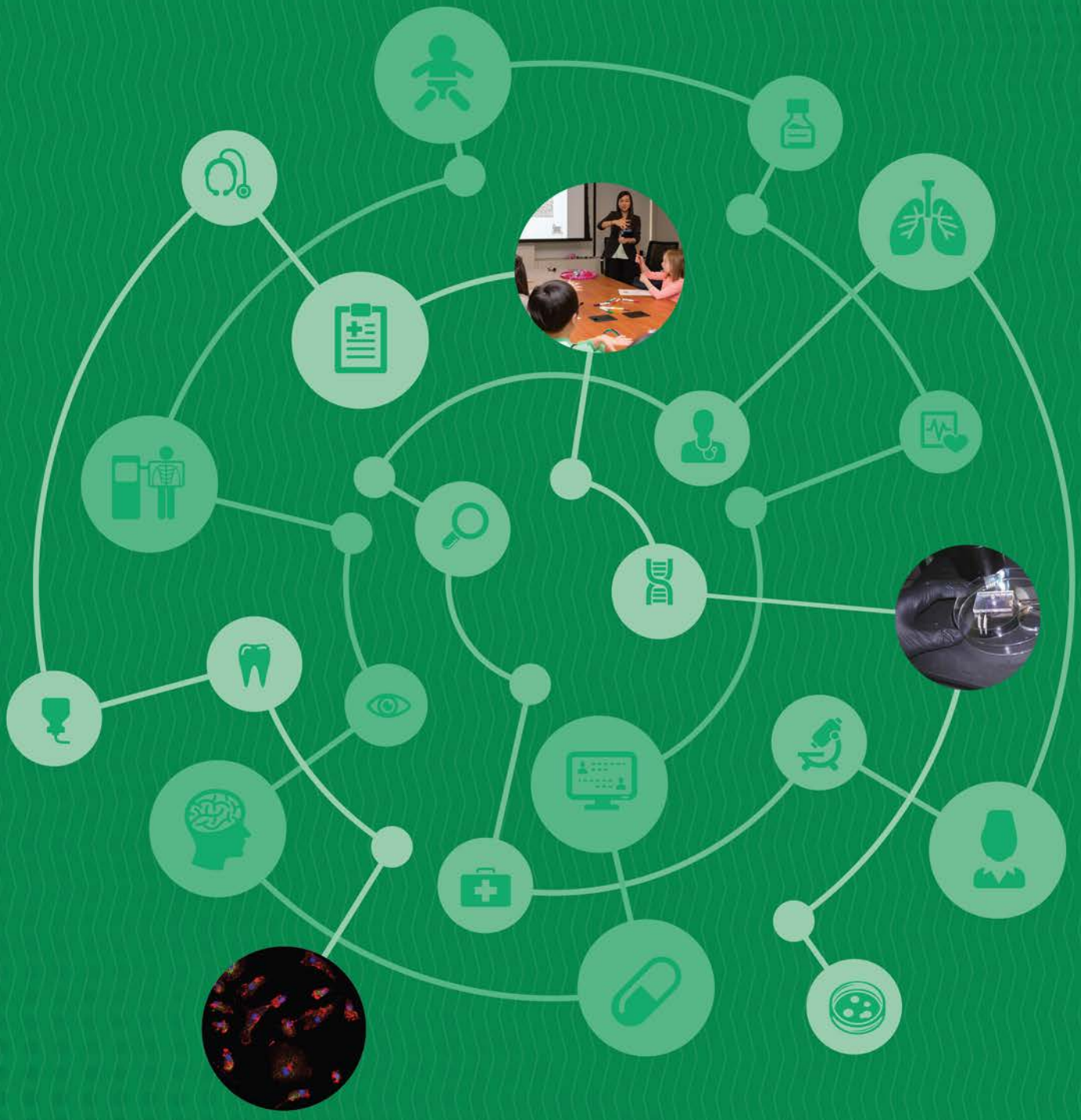
[58] http://www.nihsepa.org.
[59] http://geneed.nlm.nih.gov.
[60] http://sis.nlm.nih.gov/outreach/k12.html.

The NIDDK Short Term Research Experience Program for Underrepresented Persons (STEP-UP)[61] provides hands-on summer research experience for high school and college students interested in exploring research careers in the biomedical, behavioral, clinical, and social sciences, with an emphasis on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. STEP-UP seeks to increase participation in biomedical sciences among students from backgrounds underrepresented in biomedical research, including individuals from disadvantaged backgrounds, individuals from underrepresented racial and ethnic groups, and individuals with disabilities.

Additional resources for teachers and students include interactive online content to view and explore some of the latest bioengineering creations from NIBIB-funded research. From prosthetics to artificial kidneys, these technologies will change lives now and in the future. NIBIB also developed a *60 Seconds of Science* video series for use in high school classrooms.

NEI's *Ask a Scientist* video series is meant to inspire young people to develop an early interest in research. In each short video, an NEI scientist answers questions from middle school children on topics such as how eyes work, optical illusions, and how to become a scientist.[62]

[61] www.niddk.nih.gov/research-funding/process/diversity/research%20and-training-for-students/short-term-research-experience-underrepresented-persons/Pages/default.aspx.
[62] https://nei.nih.gov/kids.



Chapter 2: Overview of NIH Research

Introduction

NIH research focuses on both ongoing and newly emerging public health needs. In pursuit of its mission to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce illness and disability, NIH conducts and supports biomedical and behavioral research across a broad spectrum of scientific disciplines and approaches. As these needs are identified, NIH applies scientific approaches across a continuum of research designed to understand basic causes and mechanisms of disease, find new ways of identifying and interrupting disease processes, and bring these new interventions into common practice so that all may benefit. This continuum, from basic research to practice, is outlined below (and illustrated in Figure 2-1). NIH activities relating to each stage of this continuum are then described in more detail in the subsequent sections of this chapter. However, the path from basic research to clinical practice is not a continuum in the strictest sense, because all stages of the biomedical and behavioral research endeavor, 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 2-1).

Figure 2-1. *NIH Supports the Full Continuum of Biomedical Research*

Basic Research

The research continuum begins with basic research, the study of the fundamental mechanisms of biology and behavior. Investments in basic biomedical and behavioral research make it possible to understand the causes of disease onset and progression. Basic research is essential to the development of better diagnostics, the design of preventive interventions, and the discovery of new treatments and cures. Thus, basic research is a critical component of the nation's public investment in research and a central feature of NIH's research program.

Preclinical Translational Research

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

Disclaimer: Links in this chapter were last accessed on 2/11/2016.

This is an extraordinarily exciting time for advancing translational science and hastening development of new cures. Through the application of genomic research and high-throughput technologies, breakthroughs in understanding the causes of many diseases, and identifying new targets and pathways for the development of new therapeutics are within reach. Coupled with these advances, progress in technology and other fields of biomedical research have advanced the potential for developing new diagnostics and treatments for a wide range of diseases, opening a door of opportunity in translational science.

Clinical Research

Medical advances arise from rigorous testing of new strategies for recognizing and intervening in disease processes, whether intervention occurs before a disease manifests (prevention) or after it takes hold (treatment). Clinical research is patient-oriented research that is conducted with human subjects, including both studies that involve direct interaction between investigators and human subjects as well as the use of material of human origin, such as tissues, specimens, and data that retain information that would allow the investigator to readily ascertain the identity of the subject. Clinical research includes clinical trials, behavioral and observational studies, and testing and refining new technologies.

Postclinical Translational Research

In order for evidence-based research to have an impact on public health, NIH must ensure that new diagnostics and interventions reach the populations that need them most: patients, families, health care providers, and the broader public health community. The postclinical translational stage takes results from studies in humans and optimizes them to have broad applicability. NIH supports research that identifies 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.[63] Studies in this area include developing and testing novel models and methods to best implement newly discovered interventions to reach diverse groups and populations (e.g., racial/ethnic groups, rural populations).

Clinical and Community Practice

As an important part of NIH's mission, each IC engages in a broad-based effort to ensure that scientific findings are communicated rapidly and clearly to the public. However, simply communicating scientific breakthroughs and the availability of new treatments does not assure that they will be adopted in common medical practice. Nor does simply communicating research results ensure that these results will be used to inform policy-making. In addition to its communication efforts, NIH works with many partners to bring the rich evidence base of NIH research into clinical and community practice, both in treatment and prevention and in policy-making that affects public health. These partnerships include all those engaged in improving health and reducing the burdens of disease, including many federal partners both within HHS—FDA, the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ)—and outside the Department, such as the Veterans Administration (VA) and DoD. NIH also partners with nongovernmental agencies, scientific organizations, patient advocacy groups, and health care delivery systems. These partnerships provide the American public with a health care system that will enhance health, lengthen life, and reduce illness and disability.

Feedback Between Different Stages of the Research Continuum

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

[63] Within HHS, NIH and AHRQ each support health services research.

In the process of translating basic research into clinical practice, NIH supports the development of research technologies that provide innovative tools used at multiple points in the continuum and often provide the means for an exchange of information. With continued advancements in high-throughput methods, computing technologies that rapidly analyze increasing amounts of data, and interrelated bioinformatics platforms, NIH researchers across the spectrum are able to share technologies that were only dreamt of a few years ago. As biomedical research becomes more data intensive, so do the challenges for researchers to release, locate, manage, analyze, and interact with these data in the discovery and application process. To capture the opportunities and address the challenges facing all biomedical researchers, NIH has launched initiatives to increase data sharing among scientists and support new methods of managing and analyzing complex and large datasets.

Identifying Public Health Needs—Epidemiology

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

NIH Epidemiological Research Activities

Epidemiological studies examine factors that contribute to health and disease in human populations using a broad range of approaches and are a cornerstone of public health. Researchers can follow individuals or groups over time in longitudinal studies or collect a snapshot of information at a single point in time. Studies can be done retrospectively, examining outcomes that have already occurred and factors that may have contributed to health or disease, or they can be done prospectively, beginning to monitor a population of interest before a particular disease-related outcome occurs. Many epidemiological studies are observational in nature, collecting information about and comparing groups—called cohorts—made of individuals who share a characteristic of interest (e.g., tobacco use, age, educational status). Epidemiological research is important for investigating all types of disease, and it draws on expertise from a wide range of disciplines; thus, it is not surprising that virtually all NIH ICs are involved with epidemiological research in some capacity. For example, NLM supports research to develop advanced, informatics-based surveillance systems that monitor population health from a variety of sources ranging from formal clinical data to informal Internet-based newsfeeds as an innovative means for conducting public health surveillance.

Population Studies

Population studies are another type of epidemiological research, aimed at providing a better understanding of populations—how they change in size, composition, and distribution; the complex social, economic, and cultural factors that cause such changes; and the consequences of population change for health and well-being at the individual and societal levels. The population-based perspective provided by such studies often helps to form a foundation for the practical application of scientific knowledge, including changes in clinical practice and the development of public policy. For example, the Framingham Heart Study, which was initiated in 1948, linked risk of cardiovascular disease (CVD) to factors such as high serum cholesterol levels, hypertension, and cigarette smoking. Based on these results, clinicians were able not only to identify patients at high risk for CVD but also to develop interventions that reduce risk. The NIH Study of Osteoporotic Fractures finding that bone mineral density (BMD) relates closely to fracture risk contributed to Medicare's decision to pay for numerous people to get their BMD measured every two years. Many people started taking bone-preserving drugs because of the study's results, and the rate of hip fractures dropped nearly 25 percent among female beneficiaries.[64] The Osteoporotic Fractures in Men study is providing a wealth of information about steps men can take to improve their bone health.[65] The rate of hip fractures in older men also is decreasing as health care providers become more aware that fragility fractures affect patients of either sex.

In-depth understanding and monitoring of public health is a vital function of the PHS. In epidemiological research, NIH often leverages its investment by working with other agencies to collect population-based information. For example, NIDCD collaborated with CDC to incorporate several measures into CDC surveys to boost knowledge on the prevalence of hearing, balance, taste, and smell disorders. In the National Health and Nutrition Examination Survey (NHANES), NIDCD supports a hearing component (audiometry testing and related questions on hearing loss and noise exposure in adults ages 20 to 69) and a chemosenses component that consists of household interview questions with taste and smell testing. In the National Health Interview Survey, NIDCD supported development of the upcoming 2014 Hearing Supplement questions for adults 18 and older and for children younger than 18.[66, 67] The adult questions were designed to provide updated information on tinnitus (ringing in the ears), causes of hearing loss, hyperacusis (an oversensitivity to certain frequency and volume ranges of sound), exposure to noise (including firearms), use of hearing aids, wearing of hearing protection, and getting information from the Internet on hearing aid devices and hearing protection. The questions for children will ask parents about a child's use of hearing aids, hearing problems, hearing loss, ear tubes, hearing tests, exposure to loud sounds or noises, and wearing of hearing protection.

As part of the continuum from basic to applied research, epidemiological studies often test the findings of laboratory or clinical research at the population level. For example, animal studies demonstrating the reproductive and neurological effects of bisphenol A (BPA)—a common component of plastics—have prompted large-scale epidemiological studies to ascertain the exposure and health effects of this chemical in humans. Additionally, observations made through epidemiological studies often result in the formulation of new or modified hypotheses that spur new basic, translational, and clinical studies. For example, epidemiological studies in the 1950s showing that tobacco smoking increases risk of lung cancer led to extensive research to identify the carcinogens and mechanisms involved in tobacco-related carcinogenesis. Thus, epidemiological studies are essential for linking results from the bench to the patient bedside to the general population.

Longitudinal Studies

NIH has invested in many important longitudinal studies, which have yielded valuable insights. For example, NIA supports a robust portfolio of longitudinal demographic and economic research, including studies to examine the consequences of population aging and changing

[64] Brauer CA, et al. *JAMA.* 2009;301(14):1573-9. PMID: 19826027.
[65] Cauley JA, et al. *J Am Geriatr Soc* 2013;61(7):180-8. PMID: 23855842.

[66] 2014 NHIS Hearing Supplement Questions for Adult starting from page 41 of 81 to page 80 of 81. ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Survey_Questionnaires/NHIS/2014/english/qadult.pdf.
[67] 2014 NHIS Hearing Supplement Questions for Children starting from page 25 of 56 to page 50 of 56. ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Survey_Questionnaires/NHIS/2014/english/qchild.pdf.

economic circumstances on the health and well-being of older people. The NIA-sponsored Health and Retirement Study (HRS) is a premier multidisciplinary source of data on the health and well-being of older Americans, linking objective and subjective measures of health with information about retirement, economic status, family structure, and personality, as well as health behaviors and service utilization.[68] The HRS data have been used in several high-impact publications featured in top medical journals, including a recent study estimating the monetary costs of Alzheimer's disease,[69] and the study has become a model for an international collection of aging studies that support cross-national comparative research.

Two major NIAID-supported longitudinal studies continue to be an important source of data and information about many aspects of HIV/AIDS. The Multicenter AIDS Cohort Study (MACS), which began in 1984, is the longest-running HIV cohort study in the world and continues to elucidate the natural and treated history of HIV infection in men who have sex with men. The study prospectively follows thousands of homosexual and bisexual men (HIV infected and HIV uninfected but at risk) across multiple sites. The MACS has contributed significantly to the scientific understanding of HIV, AIDS, and the effects of antiretroviral therapy (ART) through more than 1,000 publications, many of which have guided public health policy and the clinical care of people with HIV. Similarly, the Women's Interagency HIV Study (WIHS),[70] which marked its 20th anniversary in 2013, is the largest and longest-running study to investigate the impact of HIV on women in the nation. The study has helped define how best to treat HIV-infected women in the U.S. and globally. The WIHS has enrolled more than 4,100 women who were HIV infected or at risk for acquiring HIV and has published approximately 600 scientific papers.

NICHD established the Pediatric HIV/AIDS Cohort Study (PHACS) in 2007 to address two critical research questions in pediatric HIV infection: (1) what the long-term safety of in utero and infant exposure to antiretroviral therapy in HIV-exposed but uninfected infants is, and (2) what the effects of perinatally acquired HIV infection in adolescents are. Approximately 10,000 HIV-uninfected infants are born to HIV-infected pregnant women every year in the U.S.; globally the number is several million. While decreasing mother-to-child transmission (MTCT) of HIV has been a major accomplishment and elimination of MTCT is now a goal of the World Health Organization (WHO), establishing the long-term safety of in utero exposure to antiretrovirals is critical. The tremendous success of combination ART has led to substantial declines in morbidity and mortality for those children who are infected perinatally. Currently in the U.S., approximately 11,000 youth were infected with HIV perinatally. The vast majority are now progressing through adolescence and entering young adulthood. Studies to monitor the long-term outcomes of lifelong HIV infection and its treatment are critical for this population, but they also will provide important information for the millions of perinatally HIV-infected children around the world who now are benefiting from access to combination ART and experiencing similar survival gains. Therefore, while PHACS is a U.S.-based network performing studies with direct relevance to the HIV-exposed, uninfected, and perinatally infected populations in this country, the knowledge gained has direct relevance for the clinical care of and the research on these populations around the world.

Epidemiological Studies in Diverse Contexts

A comprehensive understanding of health and disease requires considering factors from the molecular level to the community level. Conducting studies in diverse contexts helps to elucidate how these contributors converge to influence health and also ensures that insights gained will benefit various populations. NIH supports many 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. Three examples—the Environmental Polymorphism Registry (EPR), the Childhood Autism Risks from Genetics and Environment (CHARGE) study, and the Multi-Ethnic Study of Atherosclerosis (MESA)—illustrate NIH's pursuit to build a comprehensive understanding of health and disease.

The NIEHS-supported EPR[71] was launched to facilitate research on the interactions of genes and the environment. In collaboration with the University of North Carolina

[68] http://hrsonline.isr.umich.edu/.
[69] Hurd MD, et al. *N Engl J Med.* 2013;368:1326-34. PMID: 23550670.
[70] https://statepiaps.jhsph.edu/wihs/.
[71] http://dnaregistry.niehs.nih.gov/.

General Clinical Research Center, NIEHS has collected DNA samples from more than 17,000 individuals in the greater Research Triangle Park, North Carolina, region through local health care systems, health fairs, study drives, and other means. This region has a diverse population varying in age, ethnicity, economic and educational background, and health status. Unique features of the EPR are that participants were recruited from two distinct groups—apparently healthy individuals from the general population and patients from area clinics and hospitals—and that the EPR's DNA registry is not anonymous. This increases the likelihood of identifying subjects with both the genetic and clinical characteristics of interest and allows researchers using EPR to identify and contact registry participants (with their consent) for further study, if they are found to have potentially significant genetic variants. These aspects of the EPR give scientists the flexibility to design follow-up studies while reducing biases that can occur in genetic epidemiology studies when subjects are recruited based primarily on their observable clinical or physical traits.

Since 2006, NIEHS also has supported the CHARGE study,[72] an epidemiologic investigation of a wide spectrum of chemical and biologic exposures, susceptibility factors, and genetic interactions that may contribute to autism. The study is examining and comparing three populations of children: those with autism, those without autism but with developmental delay or mental retardation, and typically developing children. Recent research from CHARGE found evidence for a link between autism and maternal fever during pregnancy,[73] as well as that preconceptual folic acid may decrease the risk of autism in those genetically predisposed for inefficient folate metabolism.[74]

Research has shown that factors such as genetic background, geographic location, socioeconomic status (SES), and cultural traits may contribute to variations in disease risk among different populations. This observation has important implications for biomedical research, as results in one population may not necessarily apply to another. Thus, it is important to include study participants with diverse backgrounds and characteristics to increase the likelihood that insights gained through study findings will benefit all groups of people. The NIH-supported MESA[75] is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,800 men and women from four ethnic groups—white, black, Hispanic, and of Chinese ancestry. Since 1999, this study has measured and compared the value of chest computed tomography (CT), cardiac magnetic resonance imaging (MRI), carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for predicting the development of CVD. In one recent finding, researchers using a subset of the MESA cohort found that for Whites and Hispanics having more wealth, as indicated by owning a home rather than renting, was associated with better cellular health and slower aging, regardless of health behaviors.[76] This finding is consistent with other research that has shown that those with lower SES are at increased risk for age-related diseases, including CVD and cancer, which cannot be completely accounted for by poor health behaviors. Researchers have hypothesized that the other contributing factor is chronic stress from economic struggles. Chronic stress causes cumulative biological damage, mediated through inflammation and other mechanisms.

Another ongoing epidemiological initiative is NIA's Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study,[77] in which NIA intramural investigators are exploring the differences in rates and risks for diseases and other conditions associated with aging among approximately 4,000 Black and White participants of low and higher SES. HANDLS is distinctive in its use of mobile medical research vehicles, which make regular trips to participants' neighborhoods to gather data. Vitamin D deficiency is more commonly diagnosed among Blacks than in Whites; recently, HANDLS investigators found that measuring vitamin D–binding protein may be important for accurately determining vitamin D deficiency, especially among Blacks.[78]

[72] http://beincharge.ucdavis.edu/.
[73] Zerbo O, et al. *J Autism Dev Disord.* 2013;43(1):25-33. PMID: 22562209.
[74] Schmidt RJ, et al. *Am J Clin Nutr.* 2012;96(1):80-9. PMID: 22648721.
[75] http://www.mesa-nhlbi.org/.
[76] Carroll JE, et al. *Brain Behav Immun.* 2013;28:108-114. PMID: 23142704.
[77] http://handls.nih.gov/.
[78] Powe CE, et al. *N Engl J Med.* 2013;369(21):1991-2000. PMID: 24256378.

Leveraging Teams and Partnerships

Bridging the gap between research and application requires the contributions of numerous scientists with diverse expertise. Therefore, NIH fosters a culture of collaboration by encouraging researchers to build teams to conduct complex studies and analyses, as well as promoting collaborations within NIH and between NIH and other federal agencies.

The Cohort Consortium is an example of an NIH initiative that encourages a team approach to understand the role of gene-gene and gene-environment interactions in the etiology of cancer. This extramural-intramural partnership was formed by NCI to address the need for large-scale collaborations to pool the large quantity of data and biospecimens necessary to conduct a wide range of cancer studies. The Consortium includes investigators responsible for more than 40 high-quality cohorts involving more than 4 million people. The cohorts are international in scope and cover large and diverse populations. Extensive risk factor data are available on each cohort, and biospecimens, including germline DNA collected at baseline, are available on more than 2 million individuals. Investigators team up to use common protocols and methods and to conduct coordinated parallel and pooled analyses. Through its collaborative network of investigators, the partnership provides a coordinated, interdisciplinary approach to tackling important scientific questions, economies of scale, and opportunities to quicken the pace of research.

Many ICs often work together to tackle multifaceted epidemiological problems. For example, hearing loss is one of the most common birth disorders in the U.S., and Native Americans are twice as likely to have hearing loss and middle-ear infections than whites and four times more likely than other groups. Hearing loss has great significance to Native Americans due to cultural reliance on the oral communication of knowledge held by elders. In addition, alcohol use disorders are a considerable public health problem for Native Americans, and this population has some of the highest rates of fetal alcohol spectrum disorders (FASDs) in the nation. These effects can include physical problems and problems with behavior and learning, including birth defects and vision and hearing problems. NIAAA, NICHD, and NIDCD co-sponsor the Prenatal Alcohol and SIDS and Stillbirth (PASS) Network.[79] The main study conducted by the PASS Network is the Safe Passage Study,[80] which follows approximately 12,000 women from specific areas in the Northern Plains of the U.S. and the Western Cape of South Africa. In particular, NIDCD sponsors an auditory component with tests that may reveal deficits in auditory conduction and neural processing, as well as their association with maternal alcohol intake prenatally and other possible risk factors. The study also will help to improve prevention and intervention strategies that can improve the future health or lives of these high-risk newborns in Native American populations and increase knowledge about the importance of hearing screening and follow-through for underrepresented groups to ensure improved communication and occupational outcomes for these children.

Another example is the Hispanic Community Health Study, sponsored by multiple NIH ICs and offices (NHLBI, NIDCD, NIDCR, NINDS, NIDDK, and ODS), which is studying persons of Hispanic/Latino descent of diverse origins to identify factors that influence a wide variety of diseases and conditions such as heart disease, asthma, sleep disorders, diabetes, hearing loss (including noise-induced hearing loss), tinnitus, oral health, and cognitive impairment.[81] It is the largest long-term epidemiological study of health and disease ever conducted in people of Hispanic/Latino heritage living in the U.S., and the study will give particular attention to the role of cultural adaptation and disparities in the prevalence and development of disease. Between 2008 and 2011, more than 16,000 people 18 to 74 years old who self-identified as having Central American, Cuban, Dominican, Mexican, Puerto Rican, and South American origins were enrolled and examined. The second study period, from 2013 to 2019, sponsored by NHLBI and NIDDK, will continue to follow participants annually to determine changes in health. Recent findings from this study demonstrated the heterogeneity of cardiovascular disease (CVD) risk factors among people from different countries of origin. For example, Puerto Ricans carry the highest burden of CVD risk factors, while South Americans carry the lowest. Understanding this heterogeneity is critical for targeting interventions to the groups who will benefit

[79] http://www.nichd.nih.gov/research/supported/pages/pass.aspx.
[80] http://www.safepassagestudy.org/.
[81] http://www.cscc.unc.edu/hchs/.

most.[82] The insights gained from this study will be invaluable because the U.S. Hispanic population, already the largest minority population in the country, is expected to triple by 2050.

In another example, among the major collaborations of NICHD with other ICs is what is now known as the National Longitudinal Survey of Adolescent to Adult Health (Add Health), which provides investigators with unique opportunities to study how behavior, social and familial factors, environment, and health during adolescence are linked to health and achievement in adulthood. Beginning with a nationally representative sample of young people enrolled in grades 7 to 12 in the 1994–1995 school year, successive waves of interviews have collected data on respondents' social, economic, psychological, and physical well-being, combined with contextual data on the family, neighborhood, community, school, friendships, peer groups, and romantic relationships. The most recent wave of interviews expanded the collection of biological data to understand the social, behavioral, and biological linkages in health trajectories as the cohort ages through adulthood. Recent analyses of the latest Add Health data found unexpectedly higher rates of hypertension among young gay men, compared with others, that were not explained by standard CVD risk factors.[83] One group of investigators suggested that these findings may suggest disruptions in core physiological processes that ultimately confer risk for CVD that may occur early in the life course for sexual minority men.[84] In addition, Add Health's unique genetic and environmental data has been and will continue to be a major source of data for gene-environment interaction studies.

The Framingham Heart Study[85] provides an example of research that leverages past and current investments in population-based studies to study the basis of disease. The original cohort of Framingham residents was established in 1948 and has since been complemented by cohorts of their children and grandchildren. The DNA of more than 9,000 Framingham participants from all three generations has been analyzed as part of an initiative called the SNP Health Association Resource. The genetic data, along with information about major disease risk factors (e.g., systolic blood pressure, cholesterol levels, cigarette use), have been added to the database of Genotypes and Phenotypes (dbGaP), managed by the National Center for Biotechnology Information (NCBI) at NLM, and are available for use by researchers interested in investigating genetic contributors to disease.

NIH-supported studies also have been used to inform the decisions of policy-makers and assess the short- and long-term effects of policies on health or health-related behaviors. For example, in 1975, through the University of Michigan, NIDA launched the Monitoring the Future (MTF) project, a study that tracks drug use and related attitudes and behaviors of adolescents and young adults. MTF annually surveys approximately 50,000 students in grades 8, 10, and 12. MTF conducts follow-up every two years with a subset of individuals from each graduating class until they reach age 30 and then subsequently at five-year intervals. MTF data have informed policy discussions on substance abuse and have been used by the White House Office of National Drug Control Policy to monitor progress toward national health goals.[86] For example, when MTF began measuring nonmedical use of Vicodin among teens in 2002, it revealed an alarming rate of 1 in 10 high school seniors abusing this prescription pain reliever. This, along with other epidemiological research, has led to several NIDA and federal partner initiatives to address this problem, and these efforts cut that rate in half by 2013.

In another example of collaborations between NIH and another agency, NCI and the CDC National Institute for Occupational Safety and Health continue to provide data showing a statistically significant exposure-response of increasing lung cancer risk associated with increasing exposure to diesel exhaust. The study used quantitative estimates of mine workers' exposure to diesel exhaust after adjusting for other lung cancer risk factors including cigarette smoking. The findings played a pivotal role in the classification of diesel engine exhaust as carcinogenic to humans (a group 1 carcinogen) by the International Agency for Research on Cancer, part of WHO.[87, 88, 89]

[82] Daviglus ML, et al. *JAMA.* 2012;308(17):1775-84. PMID: 23117778.
[83] Everett B, et al. *J Comm Health.* 2013;38(3):588-96. PMID: 23397511.
[84] Hatzenbuehler ML, et al. *Am J Prevent Med.* 2013;44(6):612-21. PMID: 23683979.
[85] https://www.framinghamheartstudy.org/.

[86] NIDA. Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings 2008. http://www.monitoringthefuture.org/index.html.
[87] Silverman DT, et al. *J Natl Cancer Inst.* 2012;104(11):855-68. PMID: 22393209.
[88] Attfield MD, et al. *J Natl Cancer Inst.* 2012;104(11):869-83. PMID: 22393207.
[89] Stewart PA, et al. *Ann Occup Hyg.* 2012;56(4):389-400. PMID: 22383674.

Cancer is the second most common cause of death in the U.S., exceeded only by heart disease. In the U.S., cancer accounts for nearly 1 of every 4 deaths. The *Annual Report to the Nation on the Status of Cancer*,[90] released by NCI, CDC, the American Cancer Society, and the North American Association of Central Cancer Registries in December 2013, and reporting on a data period of 1975 to 2010, found a sustained fall in death rates for most cancers. The report, informed by the NCI Surveillance Epidemiology and End Results (SEER) program, found that from 2001 through 2010, death rates for all cancers combined decreased 1.8 percent per year among men and 1.4 percent per year among women. Death rates among children 14 and younger decreased 1.9 percent per year.

SEARCH for Diabetes in Youth[91] is a national multicenter study funded by NIDDK and CDC and aimed at understanding more about diabetes among children and young adults in the nation. SEARCH Study centers are located in five states: South Carolina, Ohio, Colorado, California, and Washington. SEARCH seeks answers about the types of diabetes, its complications, and how having diabetes affects the lives of children and young adults. SEARCH was launched in 2000 and will continue at least through 2015. More than 20,000 study participants representing all different racial and ethnic backgrounds have helped SEARCH determine the extent of diabetes in the community and its impact on different populations.

Initiated in 2011, the Population Assessment of Tobacco and Health (PATH) study[92] is the first large-scale NIH–FDA collaboration on tobacco regulatory research since Congress granted FDA the authority to regulate tobacco products under the Family Smoking Protection and Tobacco Control Act (2009). It is a national, longitudinal cohort study that will follow an estimated 59,000 adults and youth (12 to 18 years old)—some who use tobacco and some who do not—for at least three years. The goal of the PATH study is to assess susceptibility to tobacco use, patterns of use, risk perceptions, and resultant health impacts. The sample will include males and females of diverse racial, ethnic, and cultural backgrounds. Baseline data collection began in 2013; four or more annual data collection waves will follow. Biological specimens collected during the study (from adults only) will provide information about the health outcomes of users versus nonusers. Outcomes will further inform current and future regulatory options for FDA to protect public health, including setting tobacco product standards and communicating the risks of tobacco use to the general public.

The six-year Army Study to Assess Risk and Resilience in Service Members (Army STARRS),[93] a collaboration between NIMH and the U.S. Army, is the largest ever study of suicide and mental health among military personnel. The goal of the project is to identify, as rapidly as possible, the risk and protective factors that will help the Army develop effective strategies to reduce rising suicide rates and to address associated mental health problems among soldiers. Army STARRS' five components include historical data collected by the Army, as well as data being collected currently from soldiers in all phases of Army service. This research will help inform our understanding of suicide in the overall population, leading to more effective prevention and treatment for service members and civilians alike. The study group presented interim progress reports in meetings with the Chief of Staff, the Vice Chief of Staff, and Secretary of the Army in April and July 2013, and the group submitted the first three primary manuscripts for review.

Another example of an intergovernmental collaboration is the Agricultural Health Study, cosponsored by two NIH Institutes, NCI and NIEHS, and EPA.[94] With a cohort of more than 89,000 private and commercial pesticide applicators and their spouses, the study is exploring occupational, lifestyle, and genetic factors that may affect the disease rates in farming populations. Although current research suggests that agricultural workers are healthier overall than the general U.S. population, they may have higher rates of some types of cancer and other conditions including diabetes, asthma, neurologic disease, and reproductive problems. Recent findings from the Agricultural Health Study showed that three organophosphate insecticides and an organochlorine insecticide were significantly associated with aggressive prostate cancer.[95]

[90] http://www.cancer.gov/newscenter/newsfromnci/2013/ReportNationDec2013Release.
[91] https://www.searchfordiabetes.org/public/dsphome.cfm.
[92] https://pathstudyinfo.nih.gov/UI/HomeMobile.aspx.
[93] http://www.armystarrs.org.
[94] http://aghealth.nih.gov/.
[95] Koutros S, et al. *Am J Epidemiol.* 2013;177(1):59–74. PMID: 23171882.

Basic Research

Basic research drives progress in biomedical and behavioral sciences and is paramount in uncovering the fundamental principles of biology and, ultimately, the key to understanding health and disease. Investments in basic biomedical research make it possible to understand the causes of disease onset and progression, design preventive interventions, develop better diagnostic tests, and discover new treatments and cures. From the incremental advances in our understanding of a given disease to the groundbreaking discoveries that revolutionize our approaches for treating or preventing it, investments in basic research have yielded and will continue to yield inestimable rewards and benefits to public health.

Basic Research Lays the Foundation for Clinical Discovery and Improvements in Public Health

Basic biomedical research seeks to understand how finely tuned biological and behavioral processes work together in harmony and how these processes can break down and form the basis of disease. For example, at the molecular level, scientists' interests lie 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.

Basic research is encompassed in the missions of all NIH ICs, and progress often requires interdisciplinary approaches to develop new technologies, improve methods of data analysis, and provide insight on fundamental disease pathways. NIH fosters collaborations that span all of the traditional and emerging disciplines of the life, physical, engineering, computer, behavioral, and social sciences.

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 a continuum of collaborative interactions between research groups across multiple disciplines. The discovery of a gene that causes a disease state in mice may spark the creation of research programs to investigate the structural basis for the interaction of the gene's protein product with a partner molecule. Other studies may elucidate a novel molecular pathway that the protein and its partner molecule regulate and thereby generate a biological response. Conversely, the visualization of a previously unknown protein structure may provide remarkable insight into the protein's function and generate a hypothesis for how a particular gene mutation may generate a relevant disease model in mice. Regardless of the path to scientific advances or discoveries, basic research lays the foundation for clinical advances that improve public health. At the heart of every clinical discovery is a body of fundamental basic knowledge that provides the impetus for setting forth a clinical hypothesis and generating 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 both basic research that is related to a particular disease and other research that may be more broadly applicable (e.g., the functions of a signaling pathway). The results of basic research studies provide insights on fundamental aspects of biology and behavior and lay the foundation for other studies that will lead to ways to extend healthy life and reduce illness and disability.

Recently, NIH-supported investigators reported new breakthrough technologies including TALEN (transcription activator-like effector nucleases) and CRISPR (clustered regularly interspaced short palindromic repeats) that are having a profound impact on biomedical research and are expected to speed progress in cell-based therapies through their ability to readily modify genes inside human and model-organism cells with extreme precision. These editing methods are enabling scientists to create transgenic mice for human-disease experiments in weeks rather than months and have the potential to expedite translation of discoveries in the laboratory into future therapies for patients.

Model Organisms and Systems

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

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

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

Molecular Mechanisms and Pathways

In the human body, all biological components—from individual genes to entire organs—work together to promote normal development and sustain health. This amazing feat of biological teamwork is made possible by an array of complex molecular machinery that carries out the functions of cells and intricate and interconnected pathways that facilitate communication among genes, molecules, and cells. While some of these processes already have been discovered, many more remain to be found. Further research also is needed to understand how these processes are integrated in humans and other complex organisms, as well as to determine how disturbances in them may lead to disease and what might be done to restore disturbed pathways to their normal functions.

NIH supports a broad spectrum of research to improve the molecular-level understanding of fundamental biological processes and how to control them. By uncovering how certain molecules function in key signaling pathways, scientists may be able to develop therapies that target these molecules for the treatment of a variety of devastating disorders. The goals of research supported by NIH in this area include an improved understanding of drug action; pharmacogenetics, the study of genetic mechanisms underlying individual responses to drugs; new methods and targets for drug discovery; advances in natural products synthesis; an enhanced understanding of biological catalysts; a greater knowledge of metabolic regulation and fundamental physiological processes; and the integration and application of basic physiological, pharmacological, and biochemical research to clinical issues.

Molecular and Cell Biology

Growth and development is a life-long process that has many phases and functions. Much of the research in this area focuses on cellular, molecular, and developmental biology, to build understanding of the mechanisms and interactions that guide a single fertilized egg through its development into an adult organism. The eventual goal of these studies is to improve the diagnosis, treatment, and prevention of human genetic and developmental disorders and diseases.

All cells go through different stages in the cell cycle. A new cell is formed when its parent cell divides in two; it carries out its biological functions; it reproduces by dividing, often dozens of times; and then it dies. Underlying these milestones are regular cycles. Progress through each cycle is governed by a precisely choreographed biochemical cascade involving a repertoire of molecules. For the past several decades, NIH-supported researchers have conducted detailed studies of molecules that guide cells through division and development, methodically unraveling their biochemical identities and properties. Scientists have examined the molecules' ebb and flow throughout the cell cycle and their eventual demise as they are chemically consumed when their job is done—until generated again for the next cell cycle.

As for most life processes, when the biochemical choreography of cells goes awry, the result can be disastrous. Glitches in the cell cycle can lead to a host of diseases, most notably cancer, which can be defined simply as uncontrolled cell division and the failure of programmed cell death. Scientists are poised to take advantage of the wealth of basic research on the cell cycle. They are testing scores of potential anticancer drugs that aim to bolster or block cell cycle molecules. For instance, researchers are harnessing their knowledge of the cyclical fluctuations in cell cycle molecules to predict the aggressiveness of a cancer and to tailor treatments.

Stem Cells

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as an internal repair system, dividing essentially without limit to replenish other cells throughout life. When a stem cell divides, each new cell has the potential either to remain a stem cell or to become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a neuron.

Given their unique regenerative abilities, stem cells that are directed to differentiate into specific cell types offer the possibility of a renewable source of replacement cells and tissues to treat diseases such as diabetes, heart disease, vision loss, and Parkinson's disease. Today, donated organs and tissues may be used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Research is underway to understand how to use products developed from stem cells as therapies to treat disease. Stem cells also can be used to create cells and disease models that can be used as platforms to screen many different novel drugs, expanding the search for drug therapies and doing so with more time efficiency.

NIH has funded numerous research projects on the basic biology of human embryonic stem cells (hESCs) and has developed initiatives to support fundamental research on a new kind of stem cell called an induced pluripotent stem cell (iPSC). iPSCs are reprogrammed from adult cells to a pluripotent state remarkably like hESCs. These reprogrammed cells offer a powerful approach to generating patient-specific stem cells that ultimately may be used in the clinic. NIH has seen an increase in the number of investigator-initiated research applications using iPSCs, and NIH support for this research area continues to grow, with promising results. For example, NHLBI-funded investigators have created heart cells and heart disease models from iPSCs to determine toxicities and the potential for treatment of CVD.[96] Other ICs have had similar successes.

For neuroscientists, methods for differentiating stem cells into cells such as neurons have been cumbersome and slow, with variable results. However, NIMH-funded researchers have recently developed a shortcut to rapidly convert induced human stem cells into neurons. This breakthrough allows large-scale production of viable, induced human neurons for studying causes of brain disorders, screening potential treatments, and developing regenerative therapies.[97]

Another example of NIH investment in this area is multidisciplinary initiatives such as the NHLBI Progenitor Cell Biology Consortium (PCPB),[98] which is designed to accelerate progress in the field. PCPB tackles problems such as identifying candidate cells and directing cell differentiation and transplantation of these cells. This work could lead to the development of therapeutic cells capable of repairing damaged heart and lung tissue and replacing defective blood cells.

[96] Mordwinkin NM, et al. *JAMA.* 2013;310(19):2039-40. PMID: 24240927.
[97] Zhang Y, et al. *Neuron.* 2013;78(5):785-98. PMID: 23764284.
[98] https://progenitorcells.org/.

Immunobiology and Inflammation

The human immune system is composed of a network of specialized cells that act together to defend the body against infection by organisms such as bacteria, viruses, and parasites and to prevent cancer. Unfortunately, poorly regulated immune responses can result in the development of immune-mediated diseases that include asthma, allergy, and autoimmune syndromes such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and inflammatory bowel disease (IBD). Furthermore, the immune system of transplant recipients mounts an attack on donated organs and tissues, which imposes the need for strong drugs to prevent rejection. The lack of an immune response also can be very deleterious, increasing susceptibility to infection. Immunodeficiency disorders can be caused by inherited flaws in the immune system, as is the case with primary immunodeficiency diseases; acquired during life through infection by pathogens such as HIV that destroy immune cells; or acquired through the development of autoantibodies, which can disable immune responses.

Although much has been learned about how the immune system operates in both health and disease, there is still more to be learned that will lead to improved and novel methods to prevent or treat human disease. Thus, NIH supports basic science studies in immunobiology (the biology of the immune system) to provide a pipeline of potential new treatments and vaccines. Research in basic immunobiology focuses on the structural and functional properties of cells of the immune system and the proteins they secrete, the interactions of immune components with other physiological systems, and the processes by which appropriate regulation of the immune system is achieved to protect the body while still preventing immune attack on a person's own tissues.

Inflammation is mediated by molecules secreted by immune cells. Acute inflammation is triggered by damage to tissue or cells, typically by pathogens or injury. Chronic inflammation has been implicated in the etiology of multiple diseases, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases. Although significant breakthroughs have occurred in our understanding of inflammation, research is needed to further understand inflammatory processes. NIH is funding research to uncover as-yet-unknown immune mechanisms and mediators of inflammation, as well as genetic factors, environmental triggers, and the relationship of inflammation to disease.

One of NIH's activities in this arena is the Center for Human Immunology, Autoimmunity, and Inflammation (CHI),[99] a trans-NIH intramural initiative launched in 2008 to study the human immune system. CHI organizes integrated teams of physicians and basic scientists to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease.

"-Omics" Approaches

"-Omics" approaches characterize cellular molecules, such as genes, proteins, metabolites, carbohydrates, and lipids, and allow comparisons to be made between species and among individuals of a species. Technological advances in "-omics" have fundamentally changed the conduct of molecular biology, making it possible to rapidly obtain information on the entire complement of biomolecules within a cell or tissue. For example, it is now possible to measure the expression of all genes (transcriptome) in a cell or tissue in less than a day, something that would have taken months, if not years, just a decade ago. These advances have led to the accumulation of large datasets that scientists sift through using statistical methods, or bioinformatics, to understand how networks of cellular components work in concert to produce a state of normal health and to identify the key players that go awry as a cause or result of disease. For example, scientists may now examine the entire genome of an organism to identify genes associated with a particular trait (e.g., susceptibility to disease, developmental stage, physical trait such as height) or to compare the proteome (i.e., the entire complement of proteins) of a specific cell type with those of another (e.g., Alzheimer's brain cells vs. normal brain cells).

NIH has made a significant investment in genomics, transcriptomics, proteomics, and other types of "omics" that seek to catalog a specific class or type of biomolecule, as well as bioinformatics and computational biology.

[99] http://www.nhlbi.nih.gov/resources/chi/.

This investment has led to explosive growth in biological information, a rich resource that can be mined for clues about fundamental life processes, susceptibility to disease, and disease outcomes. The deluge of information has, in turn, generated a pressing need for computerized databases to store, organize, and index the data and for specialized tools to view and analyze the data. NIH's approach to this is discussed in the subsection on "Research Resources, Infrastructure, and Technology Development" in this section.

Genomics

As exemplified by the Human Genome Project, the field of genomics aims to understand how the entire genome, or genetic composition, of a cell or an organism contributes to define development, physiology, and disease. With a map of the human genome in hand, NIH continues to support research to understand how variations in the genetic sequence among individuals contribute to health and disease. Genomics is the study of an organism's entire genome—the complete assembly of DNA, or in some cases RNA—that transmits the instructions for developing and operating a living organism. Genomic research focuses not just on individual genes but also on the functioning of the entire genome as a network and, importantly, on how this network interacts with environmental factors to influence health and cause disease. Genomics is a new and challenging discipline that is increasingly used in virtually every field of biological and medical research. To help the public understand genomics, educational resources, including multimedia presentations, are available on the NIH website.[100]

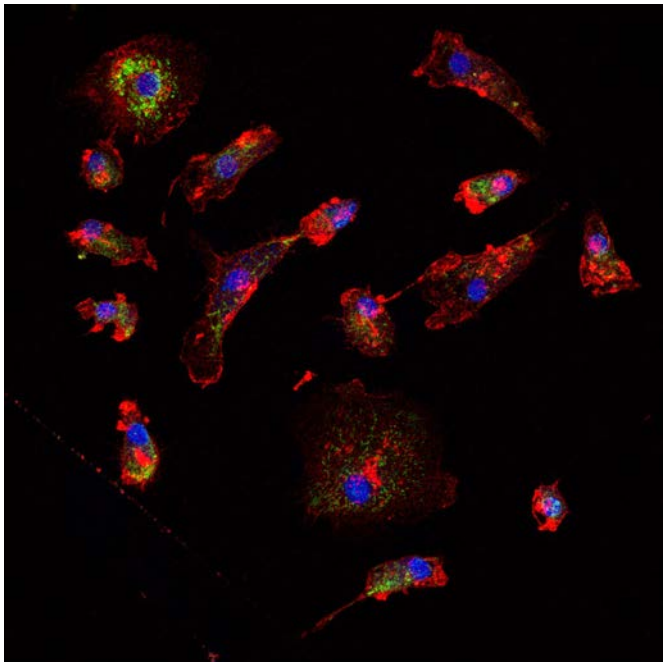


Figure 2-2. *NLRC4 mutations cause aggregation and continual activation of a cellular sensor (red) that triggers inflammation, causing an autoinflammatory disorder called macrophage activation syndrome. Credit: Kristien Zaal, Ph.D., NIAMS Light Imaging Section.*

DNA's double helical structure was discovered in 1953. Fifty years later, the human genome was fully sequenced by an NHGRI-led, multinational effort called the Human Genome Project, which lasted 13 years and completed its work ahead of schedule and under budget. The sequencing of the human genome provided new ways to analyze the functions of cells, tissues, and systems in the body and new tools for understanding the causes of disease. It laid the foundation for scientific disciplines such as proteomics, the study of the structure and function of all the proteins produced by the body (in response to instructions carried by the genes). Recent studies have demonstrated that the genome contains more information than can be interpreted from just its sequence. It is more variable in its structure and more complicated in its internal interactions than anyone imagined just a few years ago.

Almost every human disease or disorder has a genetic component and an environmental component. The genetic components of some heritable diseases, such as sickle cell disease or cystic fibrosis, result from mutations in single genes—changes that disrupt the function of the protein they encode. However, in most diseases the role of genes and the environment is more complicated. Some diseases arise as a result of spontaneous gene mutations that occur during a person's lifetime; others are caused by complex cascades of changes in gene expression triggered, perhaps, by environmental factors. Differences as small as one letter in our 3 billion pairs of DNA letters can cause disease directly or cause a person to respond differently to particular pathogens or drugs. Multiple genetic and environmental factors play a role in a myriad of common diseases and disorders, such as schizophrenia and bipolar

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

disorder; cancers of the skin, lung, brain, pancreas, breast, prostate, and testicle and acute lymphoblastic leukemia; diabetes; immunodeficiencies and allergies; periodontitis in African Americans; asthma; high blood pressure; heart arrhythmias; IBD; kidney disease; neurological diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis; and obesity. While all of the genetic risk factors are not fully understood for any of these common diseases and disorders, NIH researchers have begun to identify individual genes or regions of DNA associated with each.

As a result of the overwhelming influence of the genome on human health, virtually every NIH IC now engages in genome-related research. NIH continues to conduct exome sequencing—a technique for sequencing all the protein-coding genes in a genome, known as the exome. For example, NIAID has conducted human exome sequencing that is revealing mutations in patients with rare genetic immunological disorders.

Genes themselves, the "coding regions" of DNA that direct cells to make particular proteins, account for only about 2 percent of the human genome. Cataloging both the coding and the noncoding but functional sequences (i.e., regions that control the expression of genes) throughout the genome is the main mission of the NHGRI-funded ENCODE (ENCyclopedia Of DNA Elements) Research Consortium.[101] The project was renewed in the fall of 2012 to expand the catalogs of functional elements in the human genome, as well as in the mouse genome, which had only limited funding in the previous phase of ENCODE. The resulting list of functional elements, which includes genes and regions that control the expression of genes, is presented as a resource that is freely available on the internet.

Many ICs fund genome-wide association studies (GWAS)—in effect, full-body DNA scans (using DNA from tissue samples) that are able to identify common variants in common diseases.[102] The first successful application of GWAS was conducted in 2005 by NEI researchers in collaboration with other investigators receiving funding from several ICs. This study identified a gene variant involved in inflammation that was responsible for 50 percent of all cases of age-related macular degeneration (AMD)—a major cause of blindness in the elderly.[103] More recently, NEI also organized the largest GWAS for glaucoma, whose hereditary cause has eluded researchers, and identified two key gene variants in 2012.[104] This study was conducted by the NEIGHBOR (NEI Glaucoma Human genetics collaBORation) consortium, a NEI-funded collaborative effort to identify genetic variants associated with primary open angle glaucoma.[105] NCI also supports an array of GWAS studies, including those that recently detected new genetic factors involved in breast, prostate, and colon cancers. Across NIH, GWAS studies have identified genetic variants of many diseases and disorders, including heart disease, diabetes, obesity, IBD, and many types of cancer as previously mentioned.

Collaboration is a vital aspect of genomics research. The NIMH-funded Psychiatric Genomics Consortium (PGC),[106] which began in 2007, now boasts 123,000 samples from people with a diagnosis of schizophrenia, bipolar disorder, attention-deficit hyperactivity disorder, or autism and 80,000 controls collected by more than 300 scientists from 80 institutions in 20 countries. This consortium is the largest collaboration in the history of psychiatry. In 2012, with 14,000 cases, researchers discovered variants in 22 different genes that were significantly related to an increased risk for psychiatric illness. In 2013, with more than 30,000 cases, variants in more than 100 genes have been found to be significant, and the Cross Disorders Group of the PGC recently determined how much five major mental illnesses are traceable to the same common inherited genetic variations.[107]

The NHLBI-supported Pediatric Cardiac Genomics Consortium aims to identify genetic and epigenetic causes of congenital heart disease (CHD). A recent study from the consortium found that spontaneous mutations contribute to the development of at least 10 percent of severe CHD and that many of the mutated genes were involved in a specific pathway that controls and regulates gene expression, which provides some insight into how the defects arise.[108]

[101] http://www.genome.gov/encode/.
[102] http://www.genome.gov/gwastudies.
[103] Klein RJ, et al. *Science.* 2005;308(5720):385-9. PMID: 15761122.
[104] Wiggs JL, et al. *PLoS Genetics.* 2012;8(4):e1002654. PMID: 22570617.
[105] https://www.nei.nih.gov/funding/neighbor.
[106] http://www.med.unc.edu/pgc/.
[107] http://www.nimh.nih.gov/news/science-news/2013/new-data-reveal-extent-of-genetic-overlap-between-major-mental-disorders.shtml.
[108] Zaidi S, et al. *Nature.* 2013;498(4753):220-3. PMID: 23665959.

At the other end of the lifespan, the International Genomic Alzheimer's Project, an international collaborative initiative that includes researchers with the NIA-supported Alzheimer's Disease Genetics Consortium, completed the largest genetic analysis ever conducted in Alzheimer's disease in 2013. Analyzing data from more than 74,000 individuals from around the world, they identified 11 new genes that may be linked to late-onset Alzheimer's, the more common form of the disease. NHGRI leads the international, public-private consortium known as the 1000 Genomes Project,[109] which aims to discover almost all human genetic variants in order to support studies relating genetic variation to health and disease. So far, the project has sequenced the genomes of 1,092 people from 14 populations around the world,[110] but it aims to study more than 2,500 individuals from 26 populations. The sequence data will provide insight into the presence and pattern of variants in different people's genomes, which is vital in the effort to study the genomic basis of human disease.

NIH also is focused on sequencing nonhuman genomes. Comparing the human genome to the genomes of other creatures, including insects and even single-celled organisms, reveals stretches of DNA that have remained similar over millions of years of evolution. These "conserved" sequences are thought to play an important role in the functioning of a living organism, even if scientists do not yet know what that role is. NHGRI funded the Model ENCODE project[111] to identify all the functional elements in the genomes of two hugely important and widely used laboratory model organisms—the fruit fly *Drosophila melanogaster* and the roundworm *Caenorhabditis elegans*.[112] The strategy is to identify genomic mechanisms in these model organisms, which will elucidate novel research directions for human genomic and other researchers. The main funding phase of this project has finished with publications of results planned for 2014.

In addition, research on the genomes of pathogenic organisms will advance research on the causes, treatment, and prevention of infectious diseases. NIAID supported the sequencing of more than 40,000 genomes of pathogenic microorganisms, such as influenza, HIV, malaria, tuberculosis, and potential agents of bioterrorism such as anthrax. Data generated through NIAID-supported initiatives is made rapidly available to the research community. For example, NIAID scientists recently sequenced the genome of *Anopheles darling*, the principal malaria carrier in Central and South America and southern Mexico responsible for more than a million cases of malaria per year in the Americas.[113] NIAID scientists also sequenced the genome of *Giardia lamblia*, the most common pathogenic intestinal parasite of humans worldwide and a frequent cause of endemic and epidemic diarrhea.[114]

DNA sequencing and analysis projects serve to advance technology and bioinformatics that may soon bring revolutionary improvements to the practice of medicine. The development of new methods to sequence DNA faster and more cheaply is the central goal of some NIH-sponsored projects. Soon, when a patient's full genome can be sequenced for less than the cost of other routine medical tests, and ongoing genomic research programs have further broadened and deepened our understanding of the genome's functioning, we may well be approaching a new era in medical care. A milestone in this respect was realized in 2013 when FDA cleared the first high-throughput DNA sequencing device for clinical use.[115]

In the future, the practice of medicine will move beyond a one-size-fits-all approach, and the promise of "precision medicine" will be realized. Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. Key to the precision medicine approach is the importance of identifying genetic risk factors that affect an individual's susceptibility to developing a certain condition, and work along these lines is conducted across every IC. For example, NIDCR invests in genomic studies of tooth decay and gum disease. The aim is to provide a more complete picture of the genetic risk factors for these conditions to complement the work on behavioral, environmental, and microbial determinants. NIDCR also supports research to understand the role of genetic variation in craniofacial development and associated disorders

[109] http://www.1000genomes.org/.
[110] 1000 Genomes Project Consortium, et al. *Nature.* 2012;491(7422):56-65. PMID: 23128226.
[111] http://www.genome.gov/26524507.
[112] Celniker SE, et al. *Nature.* 2009;459(7249):927-30. PMID: 19536255.
[113] Marinotti O, et al. *Nucleic Acids Res.* 2013;41(15):7387-400. PMID: 23761445.
[114] Adam RD, et al. *Genome Biol Evol.* 2013;5(12):2498-511. PMID: 24307482.
[115] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm375742.htm.

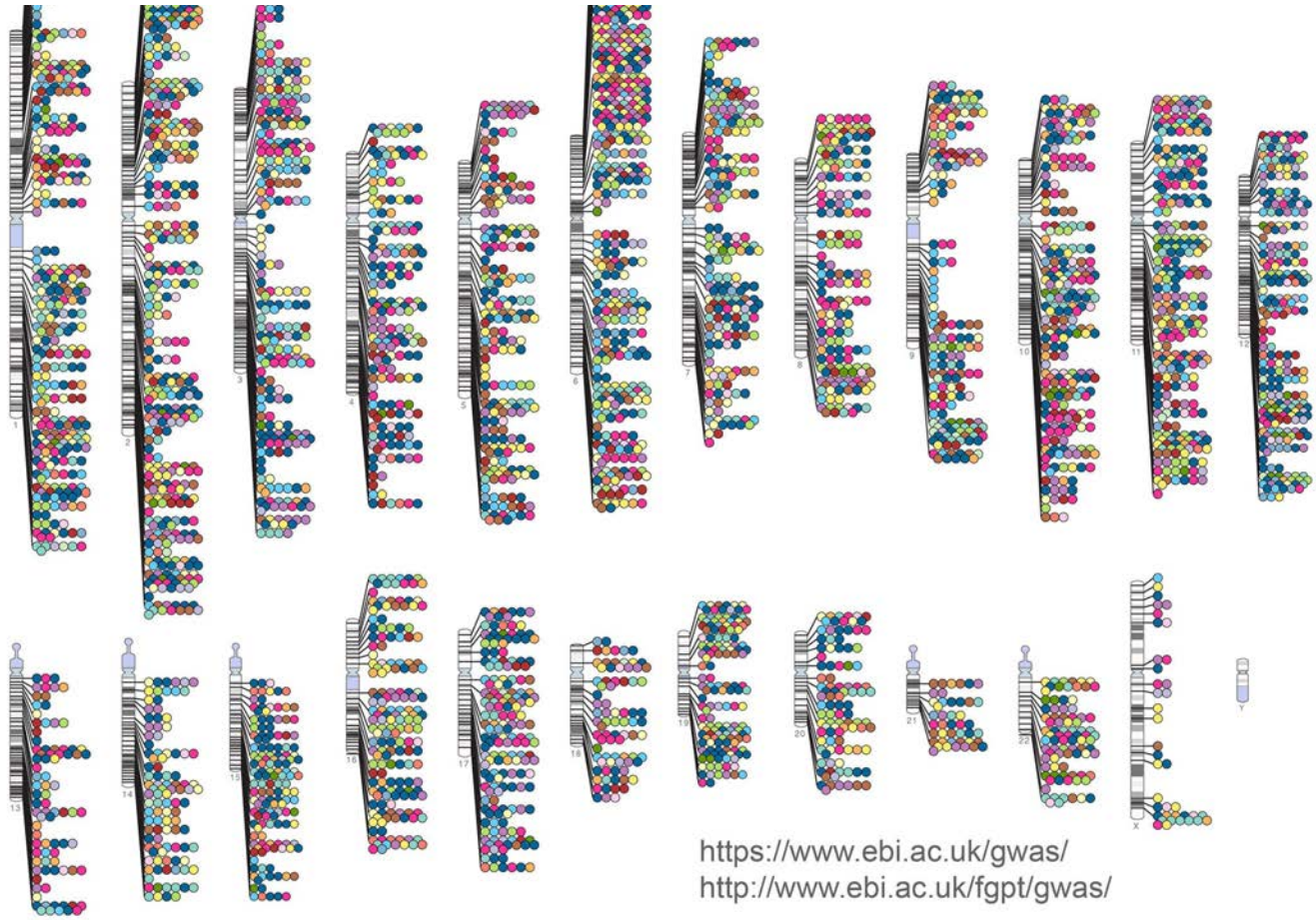


Figure 2-3. *Diagram from the NHGRI Genome Wide Association Catalog illustrating all of the disease genes that people have found using GWAS. Credit: Darryl Leja and Teri Manolio, NHGRI; Tony Burdett, Dani Welter, and Helen Parkinson, European Bioinformatics Institute.*

including Kallmann syndrome and craniosynostosis (premature fusion between bones in the skull). NIDCR-funded genomic researchers also have identified genetic risk factors for cleft lip with and without cleft palate in Asian and European ancestry populations. These investments are identifying the mechanisms of craniofacial development to allow new strategies to diagnose, treat, and, one day, prevent craniofacial disorders.

As precision medicine becomes a reality, research in pharmacogenomics seeks to understand the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a beneficial response to a drug, a poor or adverse response, or no response at all. By understanding the differences in the genetic basis of drug responses, scientists hope to enable doctors to prescribe the drugs and doses best suited for each individual. The mission of the NIH Pharmacogenomics Research Network (PGRN)[116] is to better understand the genetic basis for variable drug responses and identify safe and effective drug therapies designed for individual patients.

[116] http://www.nigms.nih.gov/Research/SpecificAreas/PGRN/Pages/default.aspx.

Another important recent finding is that one of the basic assumptions of genetic theory—that all cells of an individual have the same DNA sequence—may be an oversimplification. Called somatic mosaicism, this variability in DNA sequence from cell to cell may play an important role in brain development and in shaping an individual's susceptibility and resilience to neuropsychiatric disorders. NIMH is funding research to develop new single-cell approaches to analyze individual neuronal genomes; these tools promise to reveal new factors that contribute to neuropsychiatric diseases such as schizophrenia and autism.

Most of the genome research that will lead to direct clinical implications, improve our understanding of human health, and change clinical practice still lies ahead. Over the next decade, research will unlock the true potential of this foundational work, leading scientists closer to better means for preventing, diagnosing, and treating disease.

Epigenetics

While the genetic composition of an organism undoubtedly is an important determinant of health and disease, additional mechanisms are involved in interpreting the genome and guiding molecular, cellular, and developmental processes. In the emerging field of epigenetics, scientists are uncovering a complex code of chemical markers that influence whether genes are active or silent, independent of DNA sequence. While epigenetics refers to the study of a single gene or sets of genes, epigenomics refers to more global analyses of epigenetic changes across the entire genome. Epigenetic processes control normal growth and development and are disrupted in diseases such as cancer. Diet and exposure to environmental chemicals throughout all stages of human development, among other factors, can cause epigenetic changes that may turn certain genes on or off. Research in animal models has revealed that particular parenting behaviors trigger epigenetic changes and alterations in physiological and behavioral function of offspring. Changes in genes that would normally protect against a disease could make people more susceptible to developing that disease later in life. Researchers also believe some epigenetic changes can be passed on from generation to generation. NIH-funded scientists have demonstrated that epigenetic changes are associated with the development and growth of many types of tumors.

The Common Fund's Epigenomics Program is developing resources, tools, and technologies to enable investigations of the role of epigenomic modifications in human health and disease.[117] The Epigenomics Program has generated almost 90 reference maps of epigenomic modifications in healthy human cells and tissues, as well as numerous resources and tools that are being disseminated to and used by the biomedical research community. Researchers in the Epigenomics Program have published landmark studies on the role of epigenomic modifications in normal development and disease. In FY 2013, the Epigenomics Program launched a functional epigenomics initiative, which aims to develop novel tools and technologies to enable manipulation of the epigenome in a tissue, cell, or gene-specific fashion, with or without temporal control. Such tools and technologies are needed for precise manipulation of the epigenome in order to discover fundamental biological principles, as well as to develop novel epigenomic therapeutics.

Epigenetics research also occurs within NIH ICs. For example, NIEHS supports research on the possible effects of environmental exposures on future generations through its Transgenerational Inheritance in Mammals After Environmental Exposure program. In addition, the NIEHS Mouse Methylome Project is a cross-disciplinary effort using advanced next generation sequencing technologies, biocomputation, biostatistics, and molecular biology to create a high-resolution map of the mouse liver genome from three different mouse strains with different sensitivities to chemically induced toxicity and disease. NIEHS and NIDA also jointly fund the Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription Program, which supports research that aims to increase understanding of how exposures affect and interact with functional and regulatory processes that lead to certain patterns of epigenetic changes.

The Microbiome

The body of a healthy human adult is home to an enormous bacterial ecosystem, with bacterial cells outnumbering human cells by a factor of 10 to 1. Despite misconceptions that often associate all bacteria with disease, most of the natural bacterial flora is composed of commensal—or

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

beneficial—species that actually perform necessary cellular functions such as the digestion of certain nutrients in the intestines. However, evidence indicates that dysregulated (dysbiotic) microbial communities can contribute to such diseases and conditions as obesity, diabetes, cancer, and autoimmune diseases. Through the Common Fund and research by NIH intramural labs, the Human Microbiome Project (HMP) aims to discover the composition of microbial communities that exist in different parts of the human body and understand how these communities are associated with human health and disease.[118] In 2012, the HMP completed the initial survey of the microbiome by analyzing microbiomes from more than 300 healthy individuals, leading to the insight that there is surprising variability in microbiomes between individuals. The second phase of the HMP, launched in FY 2013, is focused on activities to create the first integrated datasets of biological properties from both the microbiome and the host using high-throughput multi-omics (transcriptomics, proteomics, metabolomics) technologies. This will enrich our understanding of how changes in the microbiome correlate with disease.

To further reveal the basic principles and mechanisms that govern the dynamics of host-associated microbial communities, many ICs including NIGMS, NIEHS, NHGRI, NIAID, NHLBI, and NIDCR support genetic, physiological, and ecological studies in an effort that will be the key foundation to developing interventions to improve human health. For example, a recent NHLBI-supported study showed that bacteria in the digestive tract metabolize the compound carnitine, found in red meat, leading to the production of a compound called trimethylamine-N-oxide (TMAO) that is linked to the development of

[118] http://commonfund.nih.gov/hmp/index.

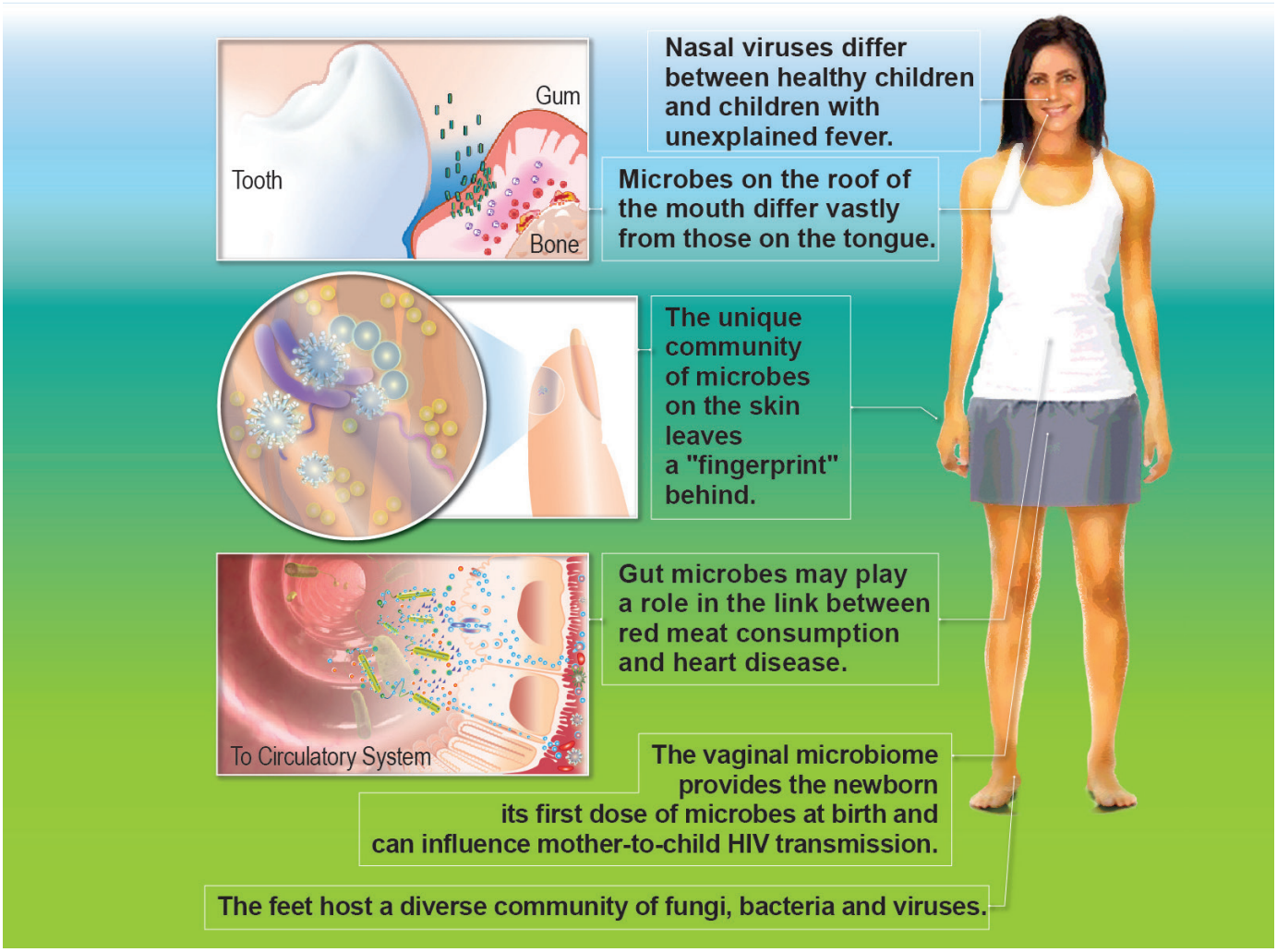


Figure 2-4. *The Human Microbiome Project examines several body sites, increasing knowledge of the impact of microbes in association with both health and disease. Credit: A Decade of Discovery—The NIH Roadmap and Common Fund.*

atherosclerosis.[119] This finding demonstrates how microbes in the gut can ultimately influence heart disease risk. In addition, NIEHS is encouraging research aimed at investigating how exposure to environmental chemicals may affect the composition and/or function of the microbiome in both the short and long term. NIEHS is particularly interested in learning about the impact of early life exposures, as these occur during the initial colonization of the microbiota and may permanently affect its potential.

NIDCR is harnessing knowledge from the HMP to define the unique role of the oral microbiota in oral diseases and immune function—such as in susceptibility to autoimmune diseases and cancer—and in other systemic conditions like metabolic syndrome. About 600 unique microbial species populate the oral cavity.[120] More than half of these species cannot be cultivated using conventional laboratory conditions, making them difficult to study and complicating scientists' understanding of how the oral microbiome functions as a whole. The NIDCR-supported open-access Human Oral Microbiome Database aims to overcome this complexity by promoting distribution of genetic, phenotypic, clinical, and bibliographic data.[121]

NIDCR clinical researchers also are studying patients with genetic defects of the immune system to understand how specific molecules and pathways control microbial interactions with the human host, in particular in the oral cavity. The systemic immune dysfunction in these patients leads to alterations in local immune response and microbial colonization and makes individuals susceptible to oral infections and inflammatory conditions such as gum disease.[122]

The NIH Microbiome Cloud Project (MCP), led by NIAID and NHGRI, addresses the opportunities and challenges posed by the explosion of data from advances in sequencing technology. The pioneering team of scientists from NIH, academia, and industry is developing a cloud-based platform that brings together HMP data on the microbes that naturally colonize our bodies and analysis tools to facilitate the growing need for large-scale data analysis. In September 2013, the first phase of the MCP was launched, which makes a 5 terabyte portion of HMP sequencing data publicly available on the Amazon Web Services cloud, thus reducing the need for time-consuming data downloads.[123] The next phase of the project will add analysis tools, more data, and supporting documentation such as online tutorials. The MCP's cloud environment promises to encourage greater collaboration and data sharing among researchers. Scientists' experiences with the MCP also will help inform NIH best practices for using cloud technologies for biomedical research.

Translating the Genetic Code: Transcriptomics, Proteomics, and Metabolomics

Beyond understanding genes and their regulation, NIH also supports system-wide studies to understand which genes are actually turned on and off and when (transcriptomics). Since genes code for the proteins that carry out almost all cellular functions, understanding which genes are active and, by extension, the catalog of proteins carrying out cellular functions (proteomics) in a given cell type under particular sets of conditions provides a picture of the molecular players involved in health and disease. In the growing field of metabolomics, researchers are using high-throughput methodologies to characterize the types and amounts of metabolic compounds present in our cells and to map the metabolic pathways and networks through which they are generated and regulated. The Common Fund's Metabolomics program, launched in FY 2012, is intended to establish the needed resources, training, technology development, and standards to catalyze the field of metabolomics to advance scientific discovery and clinical practice.[124] By studying the network of chemical pathways and their chemical products, such studies have the capability of defining normal homeostatic and disease mechanisms. Having identified pathways and compounds associated with disease progression, researchers can then use hypothesis-driven basic research experiments to further understand how particular proteins and molecules function in the pathways.

[119] Koeth RA, et al. *Nat Med.* 2013;19(5):576-85. PMID: 23563705.
[120] Dewhirst FE, et al. *J Bacteriol.* 2010;192:5002-17. PMID: 20656903.
[121] http://www.homd.org/.
[122] Moutsopoulos MD, et al. *J Autoimmun.* 2012;39(4):294-303. PMID: 22560973.
[123] http://aws.amazon.com/datasets/1903160021374413.
[124] https://commonfund.nih.gov/metabolomics/index.

Structural Biology of Proteins

In addition to understanding the collective composition of proteins in a cell, researchers also aim to characterize their three-dimensional structures. The Common Fund's Structural Biology program is a strategic effort to develop rapid, efficient, and dependable methods that can be used to determine the structure of proteins important to human health and disease.[125] Of particular interest, NIH is focusing efforts on determining structures of the proteins that reside in the membrane barrier that separates the inside of the cell from the outside. These membrane proteins account for about 30 percent of the proteins in the cell and are major targets for developing therapeutic drugs to treat particular diseases by blocking, inhibiting, or activating specific molecules. Methods developed through the Structural Biology program have resulted in the structural determination of numerous important membrane proteins, including a wide variety of G-protein coupled receptors (GPCRs), a medically important group of proteins that are the target of almost half of the pharmaceuticals on the market.

Glycomics

NIH also is mapping out additional molecular compounds associated with cellular function. In one field, NIH seeks to understand the role of glycans—complex chains of sugar molecules—in various cellular functions. Glycans often are found attached to the surface of cells and to proteins found on the cell surface, and they serve important roles in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. To advance the field of glycomics, NIH supports programs that develop technologies for the analysis of glycans in complex biological systems and has established the Consortium for Functional Glycomics,[126] which provides access to a technological infrastructure for glycobiology in support of basic research. Recent findings indicate that basic research on glycosylation may lead to the development of broad spectrum antivirals.

[125] http://commonfund.nih.gov/structuralbiology/index.
[126] http://www.functionalglycomics.org/static/consortium/consortium.shtml.

Systems Biology

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

NIGMS supports 14 multidisciplinary National Centers for Systems Biology,[127, 128] where scientists are using computational modeling and analysis to study the complex dynamics of molecular signaling and regulatory networks involved in cell proliferation, differentiation, and death; developmental pattern formation in organisms; genome organization and evolution; and drug effects on cells, organs, and tissues.

Other ICs fund research in this area. For example, investigators supported by NIAID's Systems Biology for Infectious Diseases Research Program[129] are developing and validating predictive models of infectious disease initiation, progression, and outcomes. These models will be derived from systems-wide studies of host-pathogen molecular interaction networks during infection. Importantly, the programs will make data and reagents that result from the research available to the research community. In addition, researchers in the NIAID Laboratory of Systems

[127] http://www.nigms.nih.gov/Research/SpecificAreas/SysBio/Pages/default.aspx.
[128] http://www.systemscenters.org/.
[129] http://www.niaid.nih.gov/labsandresources/resources/dmid/sb/Pages/default.aspx.

Biology[130] are applying a systems biology approach to develop models that enhance understanding of the molecular basis of an immune response to infection or vaccination. The NIH Integrative Cancer Biology Program (ICBP)[131] is providing new insights into the development and progression of cancer as a complex biological system. Researchers at ICBP Centers are generating and validating computational models that describe and simulate the complex process of cancer, which should ultimately lead to better cancer prevention, diagnostics, and therapeutics.

Environmental Factors that Impinge on Human Health and Disease

Cells not only respond to changes in their microscopic environment but also sense and respond to environmental factors present in our macroscopic human world. As part of its effort to reduce the burden of human illness and disability, NIH supports basic research to understand how environmental factors are detected by our bodies and how, at all levels—molecular, epigenetic, cellular, organ, and behavioral systems—they influence the development and progression of human diseases. At NIEHS, the IC devoted specifically to these goals, research programs are elucidating the effects of exposure to a range of toxic air pollutants in utero and resulting impaired development in fetuses and offspring, as well as increased potential for development of a range of chronic diseases later in life. Other programs are looking at the impacts of climate change on increased vulnerability of certain populations to a wide range of diseases such as cardiovascular disease, asthma, cancer, and mental disorders, as well as effects of exposure to a broad range of environmental chemicals including pesticides and endocrine disruptors. NIH also has established research programs to investigate the relationship between exposure to heavy metals, such as mercury, in the environment and the progression and development of autoimmune disorders. Understanding how these agents impart immune system dysfunction at the molecular level could offer potential therapeutic targets for treating these disorders.

[130] http://www.niaid.nih.gov/labsandresources/labs/aboutlabs/lsb/pages/default.aspx.
[131] http://icbp.nci.nih.gov/.

Basic Behavioral and Social Science Research

It has been estimated that human behavior accounts for almost 40 percent of the risk associated with preventable premature deaths in the U.S., rising to 55 percent if societal factors are taken into consideration.[132] Health-injuring behaviors such as smoking, drinking, drug abuse, as well as inactivity and poor diet, are known to contribute to many common diseases and adverse health conditions. Unfortunately, there are an insufficient number of easily implemented approaches to motivate people to adopt and maintain healthy behavior. Further, a convincing body of work including several NIA-supported studies indicates that low SES, especially low educational attainment, is associated with premature death and more disability, even after considering poor health behaviors.[133, 134] Compared to other high-income countries, Americans are less healthy—living shorter lives and experiencing more illness and injury—and a 2013 report commissioned by NIH identified both SES-related access to health care and individual behavior as contributing to this gap.[135]

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

Basic behavioral and social sciences research supported by NIH is composed of research on behavioral and social processes, biopsychosocial research, and research on methodology and measurement. Within the first category is research on behavior change, including the study of factors (e.g., cognitive, social, economic, environmental,

[132] Schroeder SA. *N Engl J Med.* 2007;357(12):1221-8. PMID: 17881753.
[133] Avendano M, et al. *Am J Public Health.* 2009;99(3):540-8. PMID: 19150903.
[134] Chapman BP, et al. *Am J Epidemiol.* 2010;171(1):83-92. PMID: 19965888.
[135] http://www.nap.edu/catalog/13497/us-health-in-international-perspective-shorter-lives-poorer-health.

developmental) that shape health decision-making and the conditions under which knowledge leads to action versus inaction. Basic behavioral economic and decision research approaches—such as *choice architecture* that describes the way in which decisions are influenced by how the choices are presented, as well as the use of financial incentives to promote behavior change—are yielding findings that may be translated into effective interventions to change behavior and improve health. Basic research on social networks is improving our understanding of how smoking and obesity spread through socially connected individuals and provides insight into how networks might be used as vehicles to spread healthy behaviors.

In 2010, the Common Fund launched the Science of Behavior Change program to promote basic research on the initiation, personalization, and maintenance of behavior change; knowledge gained through this research ultimately will be used to develop more effective and efficient behavior change interventions. In 2012 and 2013, the program held several meetings where researchers addressed topics important to advancing the science of behavior change, including how use-inspired basic research could be included in ongoing intervention research and clinical trials, and how we could better harness recent research in neuroplasticity to inform behavior change intervention.

Also launched in FY 2010, the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) is a trans-NIH initiative to pursue opportunities for strengthening basic behavioral and social science research at NIH.[136] OppNet continued to fund new work in both FY 2012 and FY 2013, including projects on the basic neurological and behavioral decision-making processes, the mechanistic pathways that link psychosocial stress and behavior.

Biopsychosocial research looks at the interaction between biological, psychological, and social processes and includes research on gene-environment interactions and other biobehavioral processes. Basic research in this area, for example, examines the processes by which the social environment, and perceived social isolation, affects physiologic processes, including gene expression. The Exposure Biology Program, of the NIH Genes, Environment, and Health Initiative, supports the development of tools to measure dietary intake, physical activity, psychosocial stress, and addictive substances—aspects of the behavioral and social environment—in addition to tools to measure environmental pollutants, for future use in studies of gene-environment interactions. Biopsychosocial research in humans and rodent models is elucidating how psychosocial stressors influence biological pathways involved in the growth and spread of cancer. Knowledge gained from biopsychosocial research will inform interventions to prevent, manage, and treat a variety of diseases and disorders.

Methodological development in the behavioral and social sciences includes a new emphasis on systems-science approaches. Much like the systems approaches to biology described above, systems science examines the multilevel, complex relationships 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 relationships of variables at multiple levels of analysis (e.g., from cells to society) simultaneously (often through causal feedback processes) while also studying impact on the behavior of the system as a whole over time. For instance, systems science methodologies are beginning to be employed for planning and preparing against acute threats to public health such as global spread of a pandemic influenza. The Models of Infectious Disease Agent Study (MIDAS) is a collaboration of nine multi-institutional research and informatics groups and two Centers of Excellence focused on developing computational models of the interactions between infectious agents and their hosts, disease spread, prediction systems, and response strategies. The models will be useful to policy-makers, public health workers, and other researchers who want to better understand and respond to emerging infectious diseases. Chronic diseases and risk factors for which systems science approaches would enhance our understanding and decision-making capacity include heart disease, diabetes, obesity, high blood pressure, eating behavior, physical activity, smoking, and drug and alcohol use.

[136] http://oppnet.nih.gov/index.asp.

Figure 2-5. *Established in 1953, the Coriell Institute for Medical Research distributes cell lines and DNA samples to researchers around the world. Shown here are Coriell's cryogenic tanks filled with liquid nitrogen and millions of vials of frozen cells. Credit: Courtney Sill, Ph.D., Coriell Institute for Medical Research.*

Research Resources, Infrastructure, and Technology Development

In building the foundation for its broad portfolio of basic research programs, NIH makes significant investments in the development of research resources, infrastructure, and state-of-the-art technologies to support its broad portfolio of basic research programs. To ensure that research resources developed with NIH funding are made readily available to the research community for further study, NIH supports multiple repositories for the collection and dissemination of animal models, cell lines, and other vital biomedical research reagents. Repositories are updated continuously as resources become available and include:

- The Mutant Mouse Regional Resource Centers,[137] which store, maintain, and distribute selected lines of genetically engineered mice
- The National Stem Cell Bank, which makes human embryonic stem cell lines readily available

[137] https://www.mmrrc.org/.

- The Beta Cell Biology Consortium,[138] which has generated animal models and antibodies that are available to the scientific community for research on type 1 and type 2 diabetes
- BIOLINCC,[139] the Biologic Specimen and Data Repository, which facilitates access to NHLBI-funded population-based biospecimen and data resources
- The NIDDK Central Repository,[140] a resource that collects samples and data from significant NIDDK studies and provides access to samples and datasets to facilitate new analyses
- The NEI-funded eyeGENE® Network database,[141] an open-access DNA repository of genetic samples from individuals and families with inherited eye disease
- The NIGMS Human Genetic Cell Repository at Coriell,[142] which houses cells and DNA representing a diverse collection of healthy individuals and individuals with various inherited diseases

[138] http://www.betacell.org/.
[139] https://biolincc.nhlbi.nih.gov/about/.
[140] https://www.niddkrepository.org/home/.
[141] https://nei.nih.gov/eyegene/FAQs_eyegene.
[142] http://www.nigms.nih.gov/Research/SpecificAreas/HGCR/Pages/default.aspx.

NIH also serves as a leading global resource for building, curating, and providing sophisticated access to imaging, molecular biology, and genomic information. In addition to databases, NIH provides resources for retrieving, visualizing, and analyzing molecular biology and genome sequence data online. NLM's NCBI is charged with creating automated systems for storing and analyzing molecular biology, biochemistry, and genomic data; facilitating the use of such databases and software by the research and medical community; coordinating efforts to gather biotechnology information both nationally and internationally; and performing research into advanced methods of computer-based information processing for analyzing the structure and function of biologically important molecules. NCBI's many genomic databases include:

- GenBank, the largest international collection of publicly available DNA sequences
- The Sequence Read Archive, which houses quadrillions of DNA bases from high-throughput sequencing projects
- The Gene Expression Omnibus repository of gene expression data
- The dbGaP of genetic association studies

More detail on NIH's efforts to develop and deploy disease registries, databases, and biomedical information systems to advance biomedical science, health, and health care is available in the section on "Harnessing Technology" in this chapter.

Preclinical Translational Research

Translating basic discoveries from the laboratory into new or more effective diagnostics and therapeutics is essential for tackling unmet biomedical needs and improving human health. However, the translational process can be complex, costly, and risk-laden, as evidenced by the less than 1 percent of compounds initially tested that actually make it into the patient's medicine cabinet. The development of medical devices, imaging techniques, and behavioral interventions follow a similar path of progression. 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. And many promising leads from basic research fail to become a proven strategy to address health, often failing in the preclinical stage.

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

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

The federal government plays a critical role in focusing on gaps in translational research that would otherwise remain unaddressed by other entities, such as pharmaceutical companies and nonprofit organizations. Specifically, NIH supports translational studies unlikely to garner substantial investment by other sources because of insufficient financial incentives, such as studies that address rare diseases, entail perceived high risk, or involve lifestyle alterations or behavioral changes. In its unique position, NIH can bring together resources that offer unprecedented opportunities. For example, NIH's ability to create consortia is particularly useful for studying rare diseases, as they make it possible to recruit sufficient numbers of participants to provide the necessary sample for preclinical and clinical study.

The Discovery of Biomarkers

Each NIH IC supports a robust portfolio of translational research that exploits basic science discoveries for the creation of new ways to intervene against specific disease processes. One important way that basic science may be used to better clinical treatment is through the identification, development, and validation of biomarkers. Biomarkers are physical, functional, or biochemical indicators of physiologic or disease processes. They play important roles in diagnosing disease, identifying patient populations that could benefit from particular therapies, and monitoring treatment effectiveness.

The Alzheimer's Disease Neuroimaging Initiative (ADNI)[143] is an example of an innovative public-private partnership to develop uniform standards for acquiring longitudinal, multisite biomarker data, including MRI, positron emission tomography (PET), cerebrospinal fluid, and blood data to characterize the progression from normal cognition to Alzheimer's disease with greater sensitivity. In 2011, the ADNI entered its second major five-year phase (ADNI 2),

[143] http://www.adni-info.org/.

focusing on participants who exhibit the very beginning stages of memory loss. One important aspect of the study is that the data will be posted to a publicly accessible database and available to qualified researchers worldwide.

Biomarkers play an important role in precision medicine; NIMH's ongoing focus on precision medicine involves using brain imaging—currently primarily a research tool—as a biomarker technology to aid clinical decision-making. Using PET, NIMH-funded researchers have identified activity patterns in particular brain regions that can predict which type of treatment (cognitive behavioral therapy and/or antidepressant medication) would be of most benefit to an individual with depression.[144] Should follow-up replication studies confirm the findings, this type of brain imaging may lead to more personalized and less trial-and-error–based treatment for depression.

Genomics Translational Research

The rapid pace of genomics research has led to a multitude of efforts to apply this understanding to the development of better ways of preventing, detecting, and treating any number of diseases and conditions.

By developing a deeper understanding of the molecular and genetic mechanisms that cause cancer, NCI is finding new ways of identifying those at risk for certain cancers and determining more precise strategies to treat those with cancer. Within its Center for Cancer Genomics, the Cancer Genome Atlas (TCGA)[145] is a multi-institutional, collaborative study conducted jointly with NHGRI that seeks to identify the changes in each cancer's genome that results in specific subtypes of that cancer. The Cancer Imaging Archive (TCIA),[146] recently established by NCI, is adding clinical imaging data from the same individuals from whom this genomic data is generated to apply advanced radiomics techniques to correlate genomics and disease type/staging with the phenotypic features visualized by clinicians through different imaging modalities. This knowledge will ultimately lay the foundation for improving cancer prevention, early detection, and treatment. The Imaging Archive recently cataloged the genetic alterations in nine important cancers for which early diagnostic methods, broadly applicable prevention strategies, and effective therapies are not yet available.

NHLBI has funded several genome consortia with strong translational components. Research focuses include identifying genetic variants that may explain why some people with asthma do not benefit from inhaled corticosteroids, identifying gene and chromosomal variations that affect pulmonary fibrosis risk and cystic fibrosis severity, improving outcome prediction for myelodysplastic syndromes, identifying genetic factors that influence blood pressure, and developing a blood test to predict the future development of diabetes.

Scientists are discovering more and more specific genetic variations that may influence an individual's response to medications. By identifying these variations, health care providers will move beyond the current one-size-fits-all approach to treatment toward prescribing drugs and dosages that are tailored to the individual's genetic make-up. A collaborative effort across several NIH ICs, the Pharmacogenetics Research Network (PGRN)[147] is helping meet the urgent need for experts in pharmacogenomics and personalized medicine by creating a nationwide network of researchers and numerous resources to facilitate their work. The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of PGRN, sponsors data sharing within and beyond the consortia. Recently, PharmGKB collaborated with several genomics groups at Stanford University to develop an integrative personal omics profile that combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody data from a single individual over a 14-month period, providing a rich data resource for numerous studies.

NHGRI is conducting a large pilot project to test ways in which high-throughput genome sequencing might be used in a clinical setting for diagnosing and treating patients. Using the NIH CC, the trial, dubbed ClinSeq (*Clin*ical *Seq*uencing), has enrolled more than 1,000 patients to date with a spectrum of coronary artery calcification, from normal to diseased, and will sequence 200 to 400 areas of their DNA that contain genes suspected of involvement in heart disease. The investigators also are working to enhance the

[144] http://www.nimh.nih.gov/news/science-news/2013/scan-predicts-whether-therapy-or-meds-will-best-lift-depression.shtml.
[145] http://cancergenome.nih.gov/.
[146] http://www.cancerimagingarchive.net/.
[147] http://www.pgrn.org/.

racial diversity of study participants by starting to recruit 500 African Americans into the project. Patients will have the option of learning the outcome of their tests, and those who carry a variant of a gene that has been linked to disease will be counseled and followed, possibly for years. The study is designed both as a pilot project to explore ways of using genome sequencing in patient treatment and as an effort to develop new data about particular genes' involvement in heart disease. The project may expand in its later stages to cover other diseases.

In a program known as the Multiplex Initiative, individuals 25 to 40 years old have been offered free testing for 15 genes associated with higher risk for type 2 diabetes, heart disease, high cholesterol, high blood pressure, osteoporosis, lung cancer, colorectal cancer, and malignant melanoma.[148] Participants were followed to see whether they changed their behavior (e.g., by adopting a healthier lifestyle or diet) in response to their test results. Interestingly, the study found that receiving the results of genetic tests did not trigger increased use of health services among the study's participants.[149]

Behavioral and Social Sciences Translational Research

Multiple efforts across NIH seek to translate basic behavioral and social sciences research into clinical interventions. For example, NIA supports the Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging.[150] The goal of the Centers is to improve the health, quality of life, and productivity of middle-aged and older people through the effective translation of basic research into practical application. Roybal investigators have developed new tools and technologies for a variety of applications, including identifying older adults at risk for automobile crash involvement and a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Investigators also have partnered with employers to test "prompts" to motivate health-related behaviors. Several Centers focus on the social network underpinnings of selected health problems affecting older people, such as obesity and cancer; develop new interventions to improve health outcomes and well-being while reducing costs; and foster translation of approaches from behavioral economics to the improvement of health care delivery for older adults.

Tissue Chips for Drug Screening

A new technology has the potential to streamline therapeutic development. Microchips lined by human cells—so called "organs-on-chips," or "tissue chips"—are bio-engineered microdevices that represent functional units of human organs, such as the lung, liver, and heart, which model both cell architecture and physiology. This novel in vitro platform could help ensure that safe and effective therapeutics are identified sooner and ineffective or toxic ones are rejected earlier in the drug development process. These tissue chips also are useful for modeling human diseases and may prove to be viable alternatives to the use of animal models.

In 2012, NIH announced new projects aimed at creating 3-D tissue chips. This new Tissue Chip for Drug Screening initiative[151] is part of a wider collaboration with DARPA and FDA. Early results indicate that these multicellular systems more closely replicate human physiology than current standard cell culture assays. The researchers are sharing resources and expertise to integrate their systems toward the objective of establishing a "human-on-a-chip."

Discovering New Therapeutic Uses for Existing Molecules

Launched in May 2012, the NCATS' Discovering New Therapeutic Uses for Existing Molecules program[152] helps re-engineer the research pipeline using an innovative strategy to identify new uses for candidate drugs that have already undergone significant research and development by industry, including safety testing in humans. This collaborative program is designed to develop partnerships between pharmaceutical companies and the biomedical research community to advance therapeutics development. By using candidate drugs that already have cleared several key steps in the development process, scientists nationwide have a strong starting point to contribute their unique expertise and accelerate the pace of therapeutics development.

[148] https://multiplex.nih.gov/.
[149] Reid RJ, et al. *Genet Med.* 2012;14(10):852-9. PMID: 22595941.
[150] http://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging.
[151] http://www.nih.gov/news/health/jul2012/ncats-24.htm.
[152] http://www.ncats.nih.gov/ntu.

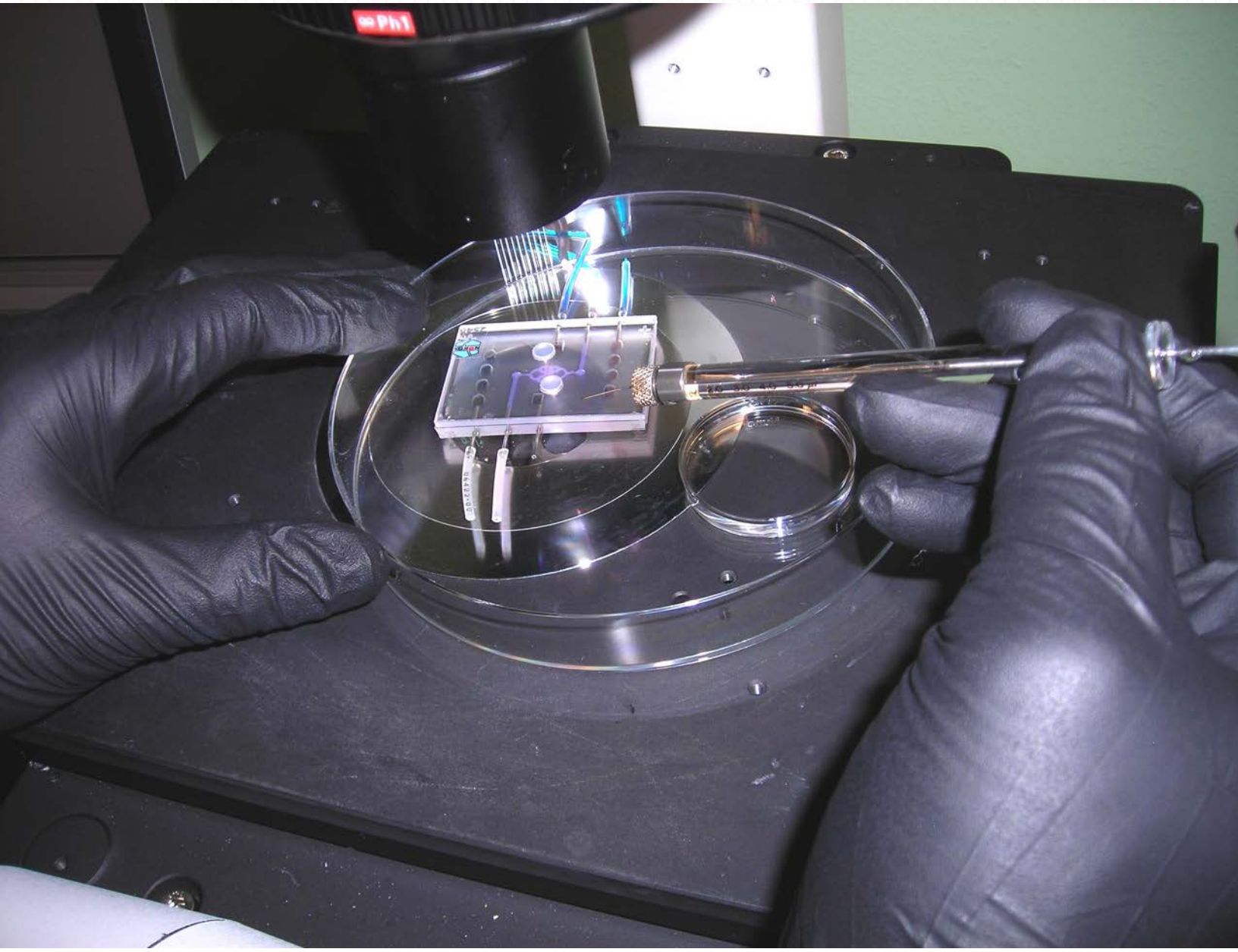


Figure 2-6. *An NIH-funded tissue chip researcher works with a kidney on a chip. Credit: University of Washington, Seattle.*

Clinical Research

NIH places a high priority on clinical research because it is the primary source of insights about new means for reducing the burden of illness and improving public health. Clinical research involves direct interaction between investigators and human subjects or the use of material of human origin, such as tissues, specimens, and data that retain information that would allow the investigator to readily ascertain the identity of the subject. Clinical research includes clinical trials, behavioral and observational studies including long-term natural history studies, and outcomes research.

At the overarching level of the NIH Office of the Director, the Office of Science Policy works on an array of issues and activities designed to harmonize regulatory aspects governing the conduct of clinical research to enhance the consistency of the rules and to ensure utmost consideration for the safety, rights, and welfare of subjects while minimizing unnecessary burdens on investigators. For

example, NIH has partnered with several federal agencies to ensure that a standard reporting format called the Basal Adverse Event Report (BAER) is available for investigators to report adverse events associated with their clinical research. The BAER is designed to simplify and streamline the submission of safety reports to multiple agencies.

Clinical trials are a crucial subset of clinical research. They are the best method of determining whether interventions are safe and effective in people and assessing side effects or other complications. They are designed to answer specific research questions about biomedical or behavioral interventions. NIH supports many types of clinical trials. Treatment trials might test experimental drugs or devices, new combinations of drugs, or innovative approaches to surgery or radiation therapy. Prevention trials look for better ways either to prevent a disease or to prevent it from returning, and they may employ research approaches assessing medicines, vaccines, and lifestyle changes, among other things. Screening and diagnostic trials are conducted to find better ways to detect or diagnose diseases or conditions, and quality-of-life trials (or supportive care trials) explore ways to improve people's comfort and ability to continue the activities of daily life, even as they deal with chronic illnesses or approach the end of life.

The translation and transfer of research knowledge and clinical trial findings into hospitals, doctors' offices, and community settings is essential if patients are to reap the benefits of clinical research. NIH nurtures strategies that bring basic research discoveries and clinical research into practice. NIH also developed an important educational site called *NIH Clinical Research Trials and You*[153] to help people learn more about clinical trials, why they matter, and how to participate (see section on "Information at the Service of Health" in this chapter).

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

Clinical Resources and Programs

The NIH Clinical and Translational Science Awards (CTSA) Program's goal is to catalyze the translation of biomedical discoveries into better health by creating an integrated research and training environment for clinical and translational sciences and support for research resources needed by local and national research communities to improve quality and efficiency across the translational research continuum. The CTSA Program, led by NCATS, seeks to develop a clinical and translational workforce with the skills and knowledge necessary to advance the translation of discoveries, promote collaboration and engagement across a broad range of investigators and stakeholders, integrate translational research within complex populations and across the lifespan, and improve research methods and processes. CTSA Program–developed methods and processes to improve translational research include ResearchMatch, a free, secure national registry aimed at improving research participant recruitment. It connects people who are looking for research studies with researchers who are seeking people to participate in their studies. Another example is REDCap, an easy-to-use, freely available tool for clinical study management and data capture that allows investigators to build and manage online surveys and databases.

A CTSA award also supported a breakthrough in brain-computer-interface research, in which a paralyzed individual was able to control a robot arm via electrodes implanted in the individual's brain.[154] A multidisciplinary team of researchers is exploring two different computerized chips that convert brain signals into an action simply through the patient's thinking about the action. Another award funded research using imaging technology to understand the brain's response to sugar. This approach could improve scientists' knowledge of the brain's role in obesity and could lead to the development of new biomarkers for the condition.

[153] http://www.nih.gov/health/clinicaltrials/index.htm.

[154] Collinger JL, et al. *Lancet.* 2013;381(9866):557-64. PMID: 23253623.

NIH Clinical Center

As mentioned in Chapter 1, the NIH Clinical Center (CC) is conducting approximately 1,500 studies at any given time. Over the years, the CC, along with its active partners and research participants, contributed to milestone achievements such as the development of chemotherapy for cancer; the first use of an immunotoxin to treat a malignancy (hairy cell leukemia); identification of the genes that cause kidney cancer, leading to the development of six new, targeted treatments for advanced kidney cancer; demonstration that lithium helps depression; the first gene therapy; the first treatment of AIDS (with the antiretroviral drug AZT); and the development of tests to detect AIDS/HIV and hepatitis viruses in blood, which led to a safer blood supply.

Along with NHGRI and the Office of Rare Diseases Research (ORDR), the CC hosts the Undiagnosed Diseases Program (UDP),[155] which has two main goals—to provide answers to patients with mysterious conditions that have long eluded diagnosis and to advance medical knowledge about rare and common diseases. Between its inception in 2008 and 2013, the UDP has received nearly 10,000 inquiries, reviewed more than 3,000 applications, and enrolled approximately 600 undiagnosed children and adults in its clinical protocols. The multidisciplinary clinical and research team diagnosed approximately 100 patients (20 to 25 percent of those evaluated), discovered two unknown diseases, and identified 15 genes not previously associated with any other human disease. A combination of genomic and clinical analyses contributed to the diagnoses. Building upon the experience and expertise of the UDP, the Common Fund launched the Undiagnosed Diseases Network in 2012 to establish clinical sites for diagnosis of rare and new diseases at academic centers across the country.[156]

A new initiative led in partnership with NICHD and several other ICs aims to make the NIH CC's research resources available to investigators outside the NIH campus by conducting research projects in collaboration with NIH intramural investigators related to the translation of basic biological discoveries into clinical applications that improve health. This program will provide access for external researchers to the NIH CC; thus, it will leverage the diverse CC resources, expertise, and infrastructure available to support studies that may not be readily supported elsewhere.[157]

Institute and Center Clinical Research Activities

Nearly all of the NIH ICs support a combination of resources, programs, and initiatives targeted toward strengthening clinical research through either the enhancement of existing capacities or the engineering of new ones. Clinical testing of novel therapies for disorders is critically important to the development of new treatments for patients and is necessary for advancing new research discoveries into clinical practice. However, clinical trials require a significant amount of administrative, financial, and scientific resources, particularly during the start-up period when the infrastructure must be established and protocols approved. NINDS is expediting this process through two clinical trials networks for neurological conditions. The Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)[158] offers shared neurology expertise and infrastructure for early stage clinical trials, including support for patient recruitment, protocol-development assistance, and a central institutional review board (IRB). The network assures broad access to these resources for testing new therapies in development by carrying out trials in partnership with industry, foundations, or academia, and the network will enable more informed decisions about which treatments to move into later stage Phase III trials. Four studies are currently underway in NeuroNEXT: one is identifying biomarkers for spinal muscular atrophy, and the others are testing new therapeutic regimens for progressive multiple sclerosis, myasthenia gravis, and severe stroke.

NINDS also supports the Neurological Emergencies Treatment Trials (NETT) network,[159] a national network of centers that perform Phase III clinical trials of treatments for neurological conditions that are commonly treated in the emergency room. Similar to NeuroNEXT, the network uses shared infrastructure and streamlined mechanisms to maximize efficiency and expedite patient recruitment into clinical trials. However, NETT is specialized to conduct trials in prehospital and emergency room settings, which

[155] http://rarediseases.info.nih.gov/research/pages/27/undiagnosed-diseases-program.
[156] http://commonfund.nih.gov/diseases/.
[157] http://grants.nih.gov/grants/guide/pa-files/PAR-13-029.html.
[158] http://www.neuronext.org/.
[159] https://nett.umich.edu/.

are complex due to special considerations regarding patient consent and the requirement for collaboration across medical disciplines, such as neurology, emergency medicine, and radiology. Since its establishment, NETT has conducted five major clinical trials in neurological diseases, including stroke, traumatic brain injury, and status epilepticus, a prolonged and life-threatening seizure.

New medications to treat mental illness are needed urgently. Existing medications can be helpful, but they often have significant limitations, in some cases requiring weeks to take effect, failing to relieve symptoms in a significant proportion of patients, or resulting in debilitating side effects. However, developing new medications is a lengthy and expensive process. Many promising compounds fail to prove effective in clinical testing after years of preliminary research. To address this issue, NIMH is working to accelerate the pace of drug discovery through an "experimental medicine" approach to evaluating novel interventions for mental illnesses. This fast-fail strategy is designed not only to identify quickly those compounds that merit more extensive testing but also to identify targets in the brain for the development of additional candidate compounds.The strategy calls for small trials focused on proof-of-concept

Figure 2-7. *NIH clinical technician with a patient using an electronic medical record. Credit: NIH.*

experimental medicine paradigms to demonstrate target engagement, safety, and early signs of efficacy. In FY 2013, NIMH launched new contracts for Fast-Fail Trials in Autism Spectrum Disorders, Mood and Anxiety Spectrum Disorders, and Psychotic Spectrum Disorders, as well as Rapidly Acting Treatments for Treatment-Resistant Depression (RAPID).[160]

NIH is working to develop policies to improve the complications that may arise from multiple institutional reviews of a single clinical protocol for multisite trials where reviews can be a barrier to the efficient and timely initiation of trials. For instance, NCI developed a central IRB initiative to improve access to NCI-sponsored trials within the National Clinical Trials Network (NCTN),[161] and now the Institute is expanding those efforts to include the Experimental Therapeutics-Clinical Trials Network with Phase I Emphasis.[162] This enables local IRBs to approve clinical trials rapidly through the use of a facilitated review process, enhance the protection of study participants by providing consistent expert IRB review at the national level, and reduce the administrative burdens associated with IRB submission on local IRB staff and investigators. Moreover, the NIH Clinical Research Policy Analysis and Coordination program is a focal point for streamlining and optimizing policies and requirements concerning the conduct and oversight of clinical research.

The NIAID Primary Immune Deficiency Clinic acts as a gateway to the NIH CC for patients with known or suspected primary immune deficiency diseases to be examined and receive a disease diagnosis and better treatment recommendations. Primary and secondary (acquired) forms of immunodeficiency result from the absence, suppression, or dysfunction of an entire set of immune cells or other immune system components. Combining clinical research with genomic sequencing technologies, NIAID and other NIH investigators are rapidly discovering, diagnosing, and treating immunodeficiencies of previously unknown cause. Intensive molecular follow-up investigation of these rare genetic disorders can elucidate fundamental biological pathways and mechanisms and lead directly to new treatment approaches. NIAID and ORDR also support the Primary Immune Deficiency Treatment Consortium, which consists of 13 major centers in North America whose shared goal is to improve the outcome of patients with rare, life-threatening, inherited disorders of the immune system.

Widespread adoption of the electronic medical record (EMR) can potentially establish new frontiers for the use of genomics in medicine. The Electronic Medical Records and Genomics (eMERGE) Network, funded by NHGRI, aims to develop, disseminate, and apply research approaches that combine the use of large DNA collections (biorepositories) with EMR systems. In doing so, this should enable large-scale, high-throughput genomic methods for use in clinical research and ongoing clinical care. eMERGE also is studying the ethical, legal, and social issues involved in the use of EMRs for genomics research, such as privacy, confidentiality, and interactions with the public. The eMERGE Network successfully accomplished its Phase I (2007–2011) aims and has entered Phase II (2011–2015). The key goal of eMERGE II is to explore the best avenues to incorporate genetic variants into EMRs for use in clinical care among diverse populations. To accomplish this, the Network expanded its member sites from five in Phase I to seven in Phase II to include racial/ethnic minorities and rural participants. The number of study participants increased from approximately 19,000 to approximately 87,000.

NIH also has specific initiatives to restructure the clinical trials enterprise in the area of oncology. For example, the Standard Terms of Agreement for Research Trials are designed to help cut the time spent on contract negotiations between pharmaceutical and biotechnology companies and academic medical centers. In addition, NCI's Clinical Trials Reporting Program is a comprehensive database containing regularly updated information, including accrual, on all NCI-supported interventional clinical trials. This information will be used to coordinate clinical research efforts to optimize the nation's investment in cancer research.

[160] http://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml.
[161] http://www.cancer.gov/clinicaltrials/nctn.
[162] http://ctep.cancer.gov/initiativesPrograms/etctn.htm.

Comparative effectiveness research (CER) improves health outcomes through the development and dissemination of evidence-based information to patients, clinicians, and decision-makers about which interventions are most effective under certain circumstances. One example of CER is that done by NHLBI's Cardiothoracic Surgical Trials Network, which was created to compare different surgical techniques and to establish evidence of effectiveness of particular surgical approaches, devices, and products for CVD. Researchers compared two different forms of coronary artery bypass graft surgery and found that, compared to the traditional open vein procedure, the less invasive endoscopic vein harvest was associated with significantly reduced wound complications.[163]

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

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

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

Inclusion of Women and Minorities in Clinical Research

The "efficacy-effectiveness" gap is a term used to show that interventions that show benefit in clinical trials do not always perform as well in the population at large. One way of decreasing the gap includes taking steps to ensure the scientifically appropriate inclusion in a given study of research participants that are representative of the population likely to use the product if it is approved. The NIH Revitalization Act of 1993 (Public Law 103-43) requires that all NIH-funded clinical research include women and members of minority groups when appropriate to the participants and the proposed research. To meet these statutory requirements, all NIH-funded clinical research is subject to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research.[164]

In accordance with the inclusion policy, applicants are required to describe what populations will be included in the proposed study, justify the exclusion of specific groups,

[163] Williams JB, et al. *JAMA*. 2012;308(5):475-84. PMID: 22851114.

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

and provide planned enrollment information. Scientific Review Groups assess proposed clinical research studies, consider whether sufficient information is provided regarding the plans for the inclusion of women and minorities, and determine whether the recruitment strategy is realistic and appropriate for the scientific goals. Investigators also are required to report annually their cumulative enrollment data by sex/gender, race, and ethnicity of participants. Inclusion enrollment data are reported biennially in aggregate in the report titled *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research* (See Appendix F).[165] The 2013 report (which covers FY 2011 and 2012) indicates that in FY 2012, women constituted 57 percent of the 17.7 million participants in clinical studies; the percentage of female participants has remained fairly stable over the previous 10-year period. In addition, 28.7 percent of participants in U.S.-based studies identified themselves as a minority.

Over the past four years, NIH has focused on streamlining the inclusion monitoring and data reporting process to reduce burden and shift the focus to better understanding how inclusion is reflected in the NIH portfolio. For example, NHLBI recently conducted an analysis of its cardiovascular clinical trials and found that in FY 2013, nearly 70 percent of participants in these trials were women, including participation in the renowned Women's Health Initiative.[166] NIH continues to emphasize the vital role of applicants, peer reviewers, funded investigators, advisory groups, and NIH staff in monitoring adherence to the NIH inclusion policy and management of grants, contracts, cooperative agreements, and intramural research projects involving NIH-defined clinical research.

[165] http://orwh.od.nih.gov/research/inclusion/reports.asp.
[166] http://www.nhlbi.nih.gov/about/directorscorner/messages/womens-health-a-legacy-of-commitment-.html.

Postclinical Translational Research

Postclinical translational research ensures that evidence-based interventions are broadly applied and accessible to those who need them most. HHS pursues this effort primarily through its support of health services research. Health services research is a multidisciplinary field, both basic and applied, that examines how social factors, organizational structures and processes, health technologies, and personal beliefs and behaviors affect access to and utilization of health care, the quality and cost of health care, and ultimately our health and well-being. The goals of health services research are to identify the most effective ways to organize, manage, and deliver high-quality care.[167] Within HHS, AHRQ has primary responsibility for health services research. NIH also supports health services research, focusing on questions that are specific to the missions of each of the ICs. In general, NIH funds health services research in which health outcomes and health-related behaviors are the primary focus and the connection between the subjects of the study and improved understanding of health are clear and explicit.

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

[167] Report of the Blue Ribbon Task Force on Health Services Research at the National Institute on Drug Abuse, 2004. Available at: https://www.drugabuse.gov/sites/default/files/files/HSRReport.pdf.

Partnering with Health Care Delivery Organizations

Health care delivery organizations are critical partners with 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 us deliver interventions faster and more effectively. An additional benefit is having access to the immense resources that health care delivery organizations offer, such as EMRs for thousands of patients. Already a number of NIH ICs support collaborative activities between health care delivery organizations, such as health maintenance organizations (HMOs), and biomedical researchers to implement large studies with real-world benefits.

The NCI Cancer Research Network (CRN) consists of the research programs, enrolled populations, and data systems of nine HMOs nationwide that, collectively, provide care to almost 10 million individuals. First funded in 1999, CRN research focuses on the characteristics of patients, clinicians, communities, and health systems that lead to the best possible outcomes in cancer prevention and care. The CRN allows for large, multicenter, multidisciplinary intervention research that addresses the spectrum of cancer control, including studies of prevention, early detection, treatment, survivorship, surveillance, and end-of-life care. The CRN also develops and uses standardized approaches to data collection, data management, and analysis across health systems. CRN activities have generated more than 295 journal publications in a range of disciplines.

A major initiative of NIMH, the Mental Health Research Network (MHRN) is a network of 13 research organizations affiliated with nonprofit health care systems serving a diverse population of 12.5 million people with mental illnesses in 15 states. In addition to providing care, these systems share rich and compatible data resources to support a wide range of effectiveness research. By linking health information databases and creating an efficient process for assessing outcomes, MHRN is working to transform the world of health care practice into a laboratory for research. For example, MHRN researchers are conducting trials to study a behavioral therapy to treat perinatal depression and a preventive suicide intervention.

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 to implement pragmatic research studies in real world health care delivery settings.[168] Led by NCCAM and NIMH, this program is providing a framework of implementation of methods and best practices that will enable the participation of many health care systems in clinical research. The Collaboratory supports the design and rapid execution of several high-impact Pragmatic Clinical Trial Demonstration Projects. The first projects, awarded in September 2012, address questions of major public health importance, including reducing health care–associated infections and hospital readmissions, improving colorectal cancer screening rates, implementing night time dosing of antihypertensive medication, examining suicide prevention strategies, examining effectiveness of epidemiological benchmarks in imaging reporting to reduce subsequent treatment, evaluating integration of psychosocial services into primary care to help patients self-manage their condition, and studying the effects of a systematic implementation of a hemodialysis session of at least four hours.

Disseminating and Implementing Clinical Research Discoveries

Dissemination and implementation research is intended to bridge the gap between clinical research and everyday practice by building a knowledge base that addresses how health information, interventions, and new clinical practices are transmitted and translated for public health and health care service use in specific settings. For example, NIDA has created two implementation infrastructures, the National Drug Abuse Treatment Clinical Trials Network (CTN) and the Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS), a multisite cooperative agreement. CTN is exemplary of efforts to translate research into practice, testing feasibility and measuring variables tied to implementation success. This research infrastructure promotes feedback from multiple

[168] http://commonfund.nih.gov/hcscollaboratory/index.

stakeholders, which is then integrated to improve drug abuse and addiction treatments, making them more feasible and readily available to those who need them. Launched in 2013, JJ-TRIALS will test different strategies for improving the delivery of evidence-based substance abuse and HIV prevention and treatment services to justice-involved youth.

Another example of bridging the gap between research and practice concerns optimizing treatments for Tourette syndrome (TS). Although TS commonly has been treated with antipsychotic medications, these medications rarely eliminate tics entirely and can cause troubling side effects such as weight gain and sedation. Consequently, many patients decline or discontinue use of these medications. Few large-scale studies have examined the effectiveness of behavioral interventions for TS until recently, when an NIMH-funded team of investigators found an effective comprehensive behavioral intervention for tics. The researchers are working with the Tourette Syndrome Association and CDC to disseminate this intervention by offering training workshops to clinicians around the country.

The NIMH Recovery After an Initial Schizophrenia Episode (RAISE) project[169] is translating evidence of treatments that have been determined to be effective into practice. In FY 2013, the RAISE Early Treatment Program completed recruitment for a large-scale practical clinical trial. The trial focused on maintaining the fidelity of the specialty care intervention as it is delivered over time and retaining individuals in treatment, as well as identifying and addressing factors that currently delay the start of effective treatment for individuals experiencing a first episode of psychosis. Results from the RAISE Connection Program informed the development of a new service initiative in New York designed to help young adults with newly emerging psychotic symptoms.

Initiated in 2005, NIDCR-supported dental Practice-based Research Networks (PBRNs) are an investigative union of practicing dentists and academic scientists. An advantage of this network is that because PBRNs address practice-based problems, their results tend to be more quickly translated into daily clinical care. The second phase of this initiative, launched in 2012, is the National Dental PBRN,[170] a seven-year project that consolidates the initiative into a unified nationally coordinated effort. The main goals of the Network are to conduct national oral health research studies in dental practices on topics of importance to practitioners, to provide evidence useful in daily patient care, and to facilitate the translation of research findings into clinical practice. The breadth of the Network allows data to be produced that can be better generalized to the highly diverse U.S. population.

NHGRI's Clinical Sequencing Exploratory Research (CSER) initiative grantees are working to address critical questions about the application of genomic sequencing to the clinical care of individual patients, from generation of genomic sequence data, to interpretation and translation of the data for the physician, to communication to the patient, including an examination of the ethical, legal, and psychosocial implications of bringing broad genomic data into the clinic. The collaborative and cooperative nature of the CSER initiative is designed to facilitate the development and standardization of best practices and common approaches to clinical translation.

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

Global Mental Health

NIMH established the Collaborative Hubs for International Research on Mental Health[171] to increase the research base for mental health interventions in low- and middle-income countries (LMICs) through integration of findings from translational, clinical, epidemiological, and/or policy

[169] http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml.

[170] http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/CurrentNewsReleases/NDPBRN.htm.

[171] http://www.nimh.nih.gov/about/organization/gmh/globalhubs/index.shtml.

Figure 2-8. National Drug Facts Week® *is a national health observance for teens to promote local events that use NIDA science to shatter the myths about drugs. Credit: Greg Gibson, 4H.*

research. The program aims to expand research activities in LMICs with the goal of providing the necessary knowledge, tools, and sustainable research-based strategies for use by government agencies, nongovernmental organizations, and health care institutions to reduce the mental health treatment gap. Lessons learned from these contexts can inform mental health service delivery in other low-resource settings.

As a group, awardees constitute a collaborative network of regional hubs for mental health research in Africa, Asia, and Latin America with capabilities for answering research questions (within and across regions) aimed at improving mental health outcomes for men, women, and children. Each hub supports research on task-shifting/task-sharing for the delivery of mental health services and provides research capacity-building opportunities. Hub teams are interdisciplinary, with strong interests in increasing the capacity of mental health services; enhancing collaborative learning and development; integrating local, state, and national health interventions; and building relationships with governmental, nongovernmental, and community-based stakeholders.

Information at the Service of Health

The main goals of NIH's information communication efforts are to broaden participation in biomedical research and to disseminate biomedical research findings with the ultimate goal of improving health outcomes—especially in medically underserved communities. It is essential that NIH's communications efforts maintain relevance and credibility with target audiences amid rapidly changing expectations and media formats. Communications products also are designed to reach audiences who are more affected by a specific health risk, disease, or disorder. Through their public information materials, campaigns and clearinghouses, NIH communications offices continue to respond to changes in health and science communications, such as how audiences obtain health and science information.

Disseminating Health Information

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

The *NIH News in Health*, a product of the NIH Office of Communications and Public Liaison (OCPL), and the *Health Information Portal* on the *Health Information* site bring the most recent and vetted health information to the public in a format that is accessible and in plain language. OCPL also produces *Research Matters*, which highlights significant science in a blog-like form that seeks to improve public understanding of current science.

In addition, information for consumers and clinicians on prevention and treatment of diseases and conditions and reviews of clinical effectiveness research are available through NLM's PubMed Health database. For example, the *NIH MedlinePlus* magazine and its bilingual Spanish counterpart *NIH Medline Plus Salud* are quarterly consumer magazines focused on bringing the latest clinical findings to patients and their families. The magazines are complementary to the *MedlinePlus*[172] and *MedlinePlus en español*[173] websites, provided by NLM, which offer trusted, consumer-oriented health information on more than 950 health topics, as well as on drugs, herbs, and supplements.

The translation and transfer of research knowledge and clinical trial findings to hospitals, doctors' offices, and community settings are of the utmost importance. NIH nurtures strategies that bring basic research discoveries and clinical research into practice. For instance, in 2013, NHLBI partnered with the American Heart Association (AHA) and the American College of Cardiology to develop CVD prevention guidelines relating to the management of high blood cholesterol, high blood pressure, and obesity. NHLBI reviewed and synthesized the evidence needed, while AHA and the American College of Cardiology developed and disseminated the guidelines.

Patient Recruitment for Clinical Trials

The public relies on physicians for information and guidance. Physicians also play a pivotal role in informing, recruiting, and enrolling participants in clinical research trials. Although volunteers in clinical research are more important than ever before, most Americans have never participated in clinical research. There are several contributing factors behind this, including:

- Many doctors do not suggest clinical research studies to their patients.
- Some individuals may not realize there are a number of possible ways they can contribute to research other than as a patient. For example, people may serve as healthy subjects or simply take a survey online.
- Potential participants may not realize they can volunteer directly to be participants in clinical research.
- Disease stigma may affect recruitment in those studies that are focused on infectious diseases or mental health conditions.
- Many people do not fully understand what a research study is or how one is carried out. Others may not trust a study's designers or how the study will be conducted. Potential participants may not be convinced of the confidentiality of individual patient data.
- Surveys have shown that most American adults have difficulty using everyday health information to make good health decisions. Information about a trial may be too technical to be easily understood, and forms, such as consent documents, may be too complicated for some individuals to understand and fill out.
- Individuals may face any number of logistical challenges, such as transportation, child care, or time constraints from shift work.

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

NIH Clinical Research Trials and You

In 2011, NIH launched the cornerstone of a new crosscutting program, a Web-based educational site called *NIH Clinical Research Trials and You*,[174] developed to help people learn more about clinical trials, why they matter, and how to participate. Resources developed for this campaign are designed to be useful to physicians both at NIH and at NIH-supported sites. The *NIH Clinical Research Trials and You* resource features information about participating in clinical trials, as well as first-hand experiences from actual clinical trial volunteers and explanations from

[172] http://www.nlm.nih.gov/medlineplus/.
[173] http://www.nlm.nih.gov/medlineplus/spanish/medlineplus.html.
[174] http://www.nih.gov/health-information/nih-clinical-research-trials-you.

researchers. The website includes links for locating or enrolling in programs; people can look for trials posted on the *ClinicalTrials.gov* website, as well as in trial registries maintained by NIH Institutes. Health care professionals can read about evidence-based strategies for talking with patients about trials, print audience-tested posters to help promote trials in clinics and offices, and find other clinical trial educational materials.

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

Highlighted Institute and Center Communication Programs

Millions of Americans search online daily for answers to health-related questions, and they look to NIH for authoritative, reliable, research-based health information. NIH communicators at the agency's 27 ICs continue to build on their evidence-based public education and awareness campaigns directed at a variety of audiences.

A list of featured health awareness, prevention, and treatment campaigns sponsored by NIH is on the NIH website.[175] Many campaigns target specific audiences for prevention and treatment efforts. Others are focused on a specific behavioral health outcome such as early diagnosis; decreased morbidity and mortality; family history, genetics, and genomics; infectious disease control and the need for vaccines; delivery of quality health care to people with special needs; diet and nutrition; and improved and refined health care practices. Several ICs, through campaigns, sponsor clearinghouses for easy access to research-based materials. A sampling of NIH campaigns and clearinghouses follows.

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

Alcohol and Other Drugs

NIAAA sponsors outreach efforts designed to address alcohol use across the lifespan. Examples include NIAAA's *Underage Drinking Research Initiative*,[176] part of which was a broad information campaign focused on preventing and reducing underage and excessive drinking among youth, and the Institute's *Rethinking Drinking* initiative,[177] which features evidence-based information about risky drinking patterns in U.S. adults, as well as support for cutting back or quitting. Given the effectiveness of screening and intervening for alcohol problems in health care settings, NIAAA continues to provide evidence-based guidelines and online training to assist health practitioners in conducting alcohol screening and brief intervention with youth and adults through its *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide* and *Clinician's Guide: Helping Patients Who Drink Too Much*, respectively. NIAAA also produces fact sheets and other resources for the general public.

NIDA sponsors several cutting-edge awareness efforts for different audiences, directed at costly nationwide problems related to drug use and addiction. One core audience for several of NIDA's campaigns is teens and the adults who live with and care for them. For example, NIDA recently updated its popular resources "Marijuana: Facts for Teens" and "Marijuana: Facts Parents Need to Know," and the Institute continues to house a robust teen website that features a blog for teens, drug facts for teens, and initiatives to educate teens on the dangers of drug use and addiction. NIDA also continues to hold its annual public health observance, National Drug Facts Week (NDFW). When NDFW began in 2010, NIDA organized 92 community events across the country to engage teens with facts about drug use and addiction. In 2013—only four years after its inception—there were more than 1,082 events held in all 50 states, in several U.S. territories, and in other countries. Every January, NIDA scientists and science writers (including the NIDA Director) participate in an annual Web chat—National Drug Facts Chat Day—with about 10,000 teens in schools from all 50 states. NIDA also promotes tools and educational resources for health care professionals through its NIDAMED initiative, designed to help clinicians

[176] http://www.niaaa.nih.gov/research/major-initiatives/underage-drinking-research-initiative.
[177] http://rethinkingdrinking.niaaa.nih.gov/.

identify patients with substance abuse problems, prevent their escalation to addiction, and refer patients to treatment as necessary. Through this initiative, NIDA developed continuing medical education courses on managing patients who use opioid pain relievers, with nearly 100,000 clinicians taking the courses for credit since its launch in late 2012.

Aging

NIA developed a national campaign, *Go4Life*, to encourage adults 50 and older to make exercise and physical activity a regular part of their everyday lives. The interactive *Go4Life* website features specific exercises, success stories, motivational tips, and nutrition information. Free materials include print publications, an exercise DVD, and online tip sheets.[178] In addition, the *NIHSeniorHealth.gov* website uses research on how older adults learn and navigate the Internet to bring them health information from NIH. Developed by NIA and NLM, *NIHSeniorHealth.gov* makes aging-related health information easily accessible for family members and friends seeking reliable, easy-to-understand online health information. The site's design and content were guided by NIA's research on the types of cognitive changes that are a part of the normal aging process.

Alzheimer's Disease

With the aging of the population, there is increasing interest in age-related cognitive decline, specifically in Alzheimer's disease. NIA's Alzheimer's Disease Education and Referral Center (ADEAR) website[179] and consumer print publications disseminated through ADEAR are the primary federal government evidence-based resource for information about cognitive decline, interventions, research, medical resources, and many aspects of care.

Cancer

NCI sponsors a number of educational and awareness efforts designed to address cancer prevention through adoption of a healthy lifestyle and diet. Through its campaigns and clearinghouses, NCI also offers cancer clinical trial resources, training programs focused on palliative and end-of-life care, and other activities and tools. Over the past decade, NCI has continued to expand its *Smokefree* campaign[180] to include Web- and mobile-based interventions to provide smokers who want to quit with access to evidence-based smoking cessation information and on-demand support. These resources include 4 websites, 6 smartphone applications, 13 social media channels, and multiple text messaging programs. Each year, millions of smokers interact with *Smokefree.gov* resources, with hundreds of thousands using these resources to successfully quit smoking. NCI also contributed Surviving Cancer, a section on the *NIHSeniorHealth.gov* website devoted to providing resources and information to older adult cancer survivors and their families.[181]

NCI also supports the National Outreach Network,[182] a multidisciplinary program that bridges NCI-supported outreach and community education efforts with cancer health disparities research and training programs. Working through community health educators, the National Outreach Network disseminates cancer information and approaches tailored to racial/ethnic communities for cancer prevention and control as well as works to enhance recruitment and retention in cancer research.

Celiac Disease

NIDDK sponsors a *Celiac Disease Awareness Campaign*[183] that provides current, comprehensive, science-based information about the symptoms, diagnosis, and treatment of celiac disease, also known as celiac sprue, nontropical sprue, and gluten-sensitive enteropathy.

Children's Health

NICHD sponsors a number of programmatic efforts to improve children's health. For parents, family members, health care providers, and caregivers, NICHD leads the *Safe to Sleep*® campaign (formerly called the *Back to Sleep* campaign), which aims to reduce the risk of sudden infant death syndrome (SIDS) and other sleep-related causes of infant death. The campaign offers information kits, professional education materials, and other resources for parents and caregivers and health care providers. The campaign also works with communities to spread messages about ways to reduce SIDS and other sleep-related causes of infant death in states and

[178] https://go4life.nia.nih.gov/.
[179] http://www.nia.nih.gov/alzheimers.
[180] http://smokefree.gov/.
[181] http://nihseniorhealth.gov/.
[182] http://crchd.cancer.gov/inp/non-overview.html.
[183] http://www.celiac.nih.gov/.

Figure 2-9. *With the goal of educating parents, family members, health care providers, and caregivers, the NICHD* Safe to Sleep® *campaign aims to reduce the risk of sudden infant death syndrome. Credit:* Safe to Sleep® *Campaign.*

counties with high rates of infant mortality and SIDS. These community-based efforts include more than 1,050 *Safe to Sleep®* Champions nationwide who are trained to help share safe infant-sleep messages with the media.

Through its *Media-Smart Youth* program,[184] NICHD is building media skills among young people to help them make more informed decisions about nutrition and physical activity. This evidence-based 10-lesson curriculum teaches tweens and teens how to think critically about media images and messages so they can make better decisions about the foods they eat and the activities they do. It also encourages participants to reduce sedentary "screen time," a known contributor to obesity and other health problems. The program is exploring a "teen leader" mechanism to encourage teens, under supervision of an adult and under the guidance of a local health organization, to conduct the program with middle school students as a way to improve children's health in communities.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the U.S. and is estimated to affect 24 million people across the nation, with as many as half undiagnosed. To address this serious lung disease, NIH developed the *COPD Learn More Breathe Better®* education initiative.[185] The program is designed to help at-risk men and women older than 45 recognize the signs and symptoms of COPD and encourages them to talk with their health care providers about testing and treatment options. The program also educates health care providers about the prevalence of COPD, which patients are at risk for the disease, early detection methods, and treatment options. Through a network of more than 80 national and local partners conducting COPD outreach in all 50 states and the District of Columbia, the program sponsors community-level outreach and events, media outreach efforts, social media strategies, and development of robust partnerships.

Diabetes

In collaboration with more than 200 public and private partners, NIDDK and CDC co-lead the National Diabetes Education Program (NDEP),[186] which disseminates evidence-based educational materials on diabetes. For example, the NDEP encourages people to take "small steps" to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in its *Control Your Diabetes. For Life.* educational campaign.[187] Campaign materials are tailored for minority groups at high risk of developing type 2 diabetes. NIDDK's National Diabetes Information Clearinghouse also provides key health information for patients, health care professionals, and the general public.

[184] https://www.nichd.nih.gov/msy/Pages/index.aspx.

[185] http://www.nhlbi.nih.gov/health/educational/copd/lmbb-campaign/.
[186] http://ndep.nih.gov/.
[187] https://www.niddk.nih.gov/health-information/health-communication-programs/ndep/partnership-community-outreach/campaigns/small-steps-big-rewards/Pages/smallstepsbigrewards.aspx.

Environmental Health

The NIEHS-led Partnerships for Environmental Public Health (PEPH) program[188] focuses on conducting and translating research into action to address the effects of environmental exposures and health risks of concern to the public and particularly affected communities. PEPH is a network that brings together scientists, community members, educators, health care providers, public health officials, and policy-makers in the shared goal of advancing the impact of environmental public health research at the local, regional, and national levels.

Eye Health and Vision

The NEI *National Eye Health Education Program*[189] (NEHEP) aims to increase awareness of science-based information to prevent and treat diabetic eye disease, glaucoma, low vision, and age-related eye diseases and conditions. A series of educational materials, websites, and social media resources (all available in English and Spanish) are available to the public and targeted to at-risk populations. NEHEP also develops teaching tools and webinars for health professionals and community health workers. Additionally, NEI's *Healthy Vision Program*[190] provides the public with general eye health information and promotes the importance of comprehensive dilated eye examinations and eye safety.

Hearing

In October 2008, NIDCD launched *It's a Noisy Planet. Protect Their Hearing*.[191] The *Noisy Planet* campaign is designed to increase awareness among parents of children 8 to 12 years old ("tweens") about the causes and prevention of noise-induced hearing loss. With this information, parents and other educators and health professionals can encourage children to adopt healthy habits that will help them protect their hearing for life. In 2013, NIDCD completed an evaluation of the *Noisy Planet* campaign. The evaluation showed that the campaign's message and materials are useful and effective and reach the campaign's target audiences. The evaluation also highlighted the need for more promotional tools to encourage healthy hearing behaviors and efforts to reach a broader segment of the U.S. population.

Health Disparities and Minority Health

The NIAMS *National Multicultural Outreach Initiative*[192] aims to help address disparities in the availability and access to research-based and culturally relevant health information among various multicultural groups. Through the development and distribution of culturally targeted health planners and health information in multiple languages (Spanish, Chinese, Vietnamese, Korean), people from multicultural backgrounds who have diseases and conditions of the bones, joints, muscles, and skin can learn about available resources from NIAMS, NIH, and other federal agencies that can help people cope with their chronic disease or condition to improve their quality of life.

NIAMS also leads the Trans-NIH American Indian and Alaska Native Health Communications and Information Work Group, which coordinates efforts to develop and disseminate health information targeting those respective communities. It partners with the Indian Health Service to disseminate NIH information kits to approximately 1,600 American Indian and Alaska Native community health representatives. Since the inception of the project in January 2008, NIH has sent more than 13,000 information kits to community health representatives on topics such as arthritis, bone health, cancer, diabetes, drug abuse prevention, mental health, and heart health.

NLM develops culturally appropriate websites that focus on information to address health disparities among special populations. The American Indian Health Web Portal[193] is dedicated to issues affecting the health and well-being of all North American Indians and includes current research information and traditional healing resources. The Arctic Health website,[194] in collaboration with the Alaska Medical Library at the University of Alaska, Anchorage, brings together reliable information on diverse aspects of the Arctic environment and the health of northern peoples. The *Asian American Health* website[195] addresses the needs of the diverse communities of Asian Americans in the U.S.

The NLM Exhibition Program presents exhibitions on current and historical topics in medicine. The *Native Voices: Native Peoples' Concepts of Health and Illness* exhibition,

[188] http://www.niehs.nih.gov/research/supported/translational/peph/.
[189] http://www.nei.nih.gov/NEHEP.
[190] https://www.nei.nih.gov/healthyeyes/.
[191] http://www.noisyplanet.nidcd.nih.gov/Pages/Default.aspx.
[192] http://www.niams.nih.gov/multicultural/.
[193] http://americanindianhealth.nlm.nih.gov.
[194] http://arctichealth.nlm.nih.gov/.
[195] http://asianamericanhealth.nlm.nih.gov/.

Figure 2-10. *NIDCD* Noisy Planet *team member Phalla Keng demonstrates how loud noise can damage hair cells. Credit: NIDCD.*

which examines concepts of health and medicine among contemporary American Indians, Alaska Natives, and Native Hawaiians, opened at NLM in FY 2012.[196] This exhibition, developed in consultation with native leaders in Alaska, Hawaii, and the contiguous U.S., honors the native tradition of oral history and includes a unique collection of information. The exhibition explores the interconnectedness of wellness, illness, and cultural life through interviews with native people, artwork, cultural objects, interactive media, and a healing totem created for the exhibition. An iPad app also allows remote exploration of the content of the exhibition, including hearing the voices of the individuals who were interviewed.

Heart Health

To make women more aware of the danger of heart disease, NHLBI partners with many national and community organizations to sponsor a national campaign called *The Heart Truth®*.[197] The program's goal is to raise awareness

[196] http://www.nlm.nih.gov/nativevoices/.

[197] http://www.nhlbi.nih.gov/health/educational/hearttruth/.

about heart disease and its risk factors among women and educate and motivate them to take action to prevent the disease and control its risk factors. Consistent with its goal, *The Heart Truth®* has contributed to an increased awareness among women that heart disease is their leading cause of death; a 2012 AHA survey showed that such awareness nearly doubled over the past 12 years, from 30 percent to 56 percent.

HIV/AIDS

OAR supports working groups of clinical experts who develop federal guidelines for the use of antiretroviral treatment for the management of HIV in adults, adolescents, and children and for the prevention of perinatal transmission, as well as guidelines for the treatment and prevention of HIV complications and opportunistic infections. These guidelines are updated regularly and disseminated widely to health care providers and patients through the *AIDSinfo* website.[198] The website also includes information on clinical trials for HIV treatment and prevention; information on approved drugs for HIV infection; and HIV-related information for health care providers and patients, which also can be accessed by phone, online, or mobile application. The website is managed by NLM with support from OAR and NIAID.

Kidney Disease

NIDDK also fosters education and outreach campaigns to spread the evidence-based information about how people can prevent kidney disease and preserve kidney function. For example, NIDDK's National Kidney Disease Education Program[199] raises awareness about the problem of kidney disease and steps such as control of diabetes or high blood pressure that should be taken to treat chronic kidney disease and prevent kidney failure. It represents a major educational outreach effort to patients, physicians, and the public and includes materials tailored to minority groups at high risk.

Mental Health Outreach

The Outreach Partnership Program is a nationwide initiative of NIMH's Office of Constituency Relations and Public Liaison. The Program works to increase the public's access to science-based mental health information through partnerships with national and state organizations. The Program encourages efforts to reach diverse racial and ethnic groups. The Program also strives to enhance opportunities for the public to benefit from participation in research. These partnerships provide NIMH with the opportunity to engage community organizations in dialogue to better understand the needs, questions, and concerns of those intended to benefit from the research the Institute supports.

Oral Health

An important part of the NIDCR mission is promoting the timely transfer of knowledge gained through research and its implications for health to the American public. An Institute priority is outreach to fast-growing demographic groups and underserved communities that have uneven access to understandable information about oral health. For Hispanics/Latinos, NIDCR has expanded its Spanish-language oral health information offerings and continues to update and maintain its Spanish-language website, which consistently receives high customer satisfaction scores.[200] For the aging population, the Institute has created new oral health content tailored for older adults. NIDCR has partnered with NIA and NLM on oral health modules for the *NIHSeniorHealth* website[201] and with HHS to create oral health content for older adults for *Healthfinder.gov*.[202] Under the auspices of HHS, NIDCR is also a *Text4baby* partner.[203] Through *Text4baby*, pregnant women and new moms receive free text messages about a range of health topics, including oral health. *Text4baby* reaches a higher proportion of women in underserved communities than in the general population.

Stroke

NINDS continues to develop and manage the Institute's groundbreaking public education campaign *Know Stroke: Know the Signs. Act in Time*.[204] The campaign was designed to help increase knowledge and awareness about the early warning signs and symptoms of stroke and to drive behavior change, especially in at-risk communities. It includes outreach to consumers and health care

[198] http://www.aidsinfo.nih.gov/.
[199] http://nkdep.nih.gov/.
[200] https://catalog.nidcr.nih.gov/OrderPublications/default.aspx#11.
[201] https://nihseniorhealth.gov/periodontaldisease/whatisgumperiodontaldisease/01.html.
[202] http://healthfinder.gov/HealthTopics/Population/older-adults/health-conditions-and-diseases/oral-health-for-older-adults-quick-tips.
[203] https://www.text4baby.org/.
[204] http://www.stroke.nih.gov.

professionals using mass media, social media, grassroots partnerships, and community education. The foundation for this initiative is community engagement in "train the trainer" programs. These programs in major urban areas across the U.S. use NINDS materials to educate local high-risk audiences, including African Americans, Hispanics, and people older than 50 and their family members, caregivers, and health care providers. NINDS also has partnered with the General Federation of Women's Clubs to create a nationwide network of volunteers and with the National Council of La Raza to develop and promote culturally appropriate materials for Hispanic Spanish-speaking audiences including a video, flipchart, and educational toolkit.[205] NINDS has partnered with AHA to coordinate a national distribution of the Spanish language toolkits. In addition, NINDS partnered with CDC to develop and distribute a brochure called *What You Need to Know About Stroke*, which was developed for African Americans.

[205] http://stroke.nih.gov/espanol/.

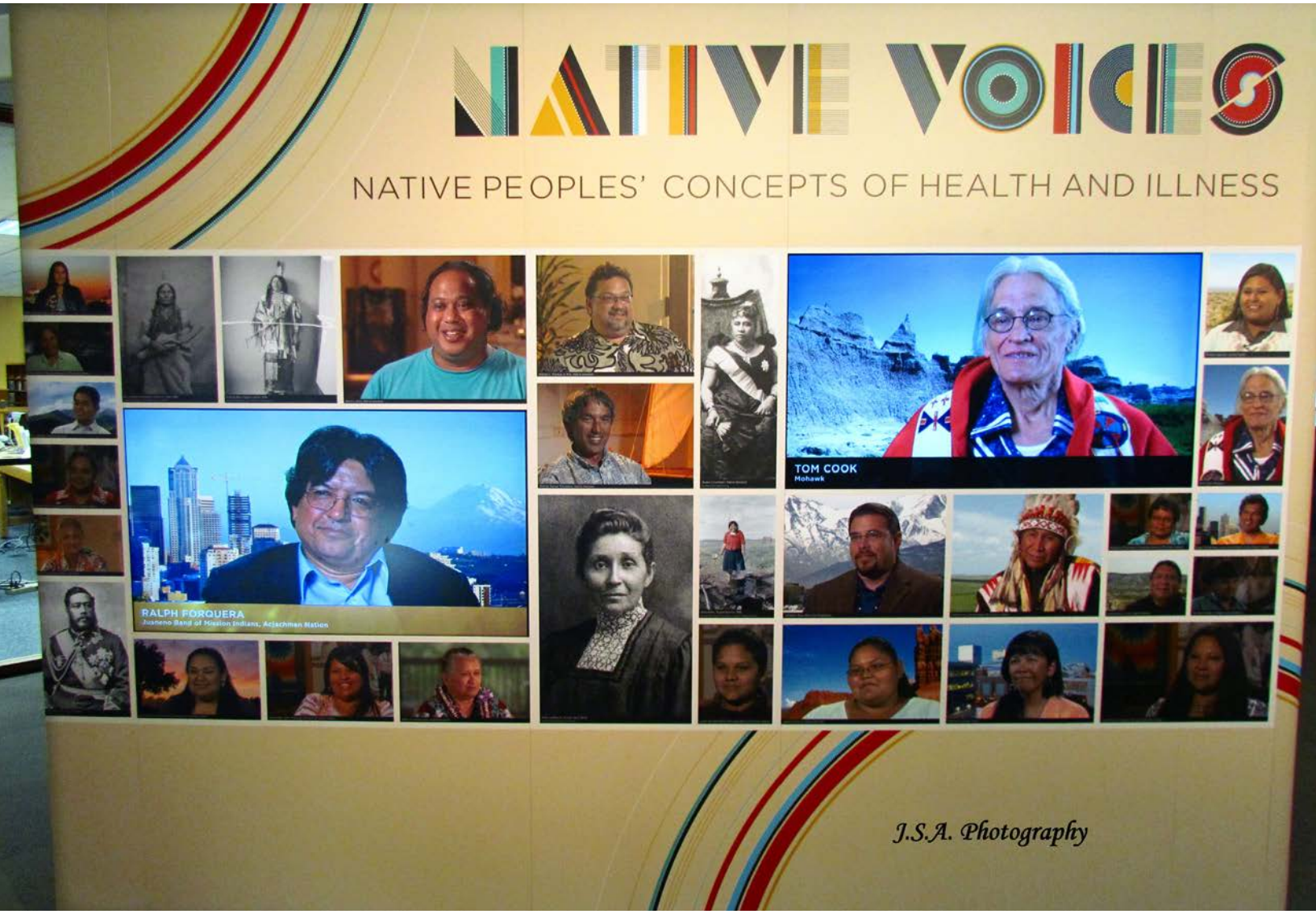


Figure 2-11. *Entrance to the* Native Voices *exhibition at NLM. Credit: J.S.A. Photography.*

Complementary and Integrative Health Practices

NCCAM provides objective, evidence-based information on the safety and efficacy of complementary and integrative health practices to scientists, health care providers, and the general public through a variety of approaches, including emerging technology and platforms (i.e., video, social media, and mobile applications) and an information-rich website.[206] For example, NCCAM publishes the *Clinical Digest*, a monthly e-newsletter that summarizes the state of the science on complementary health practices and clinical guidelines.[207] Additionally, NCCAM provides an online resource that enables health care providers to make informed recommendations.[208]

[206] http://nccih.nih.gov.
[207] http://nccih.nih.gov/health/providers/digest.
[208] http://nccih.nih.gov/health/providers/.

Harnessing Technology

In today's world, technology advances at an unprecedented pace. NIH is in step with this technological revolution in multiple ways, from fostering new technological advances for rapid data collection and sharing huge amounts of data, to developing new technologies to better detect and treat numerous diseases and disorders, to ensuring that research results—from scientific publications to patient and consumer health information—are readily available to all.

NIH supports technology development through several complementary approaches, including:

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

NIH support of technology development continues to drive our understanding of health and disease. In recent years, biotechnology and nanotechnology have undergone extensive development and expansion. Biotechnology combines disciplines such as genetics, molecular biology, biochemistry, embryology, and cell biology, which in turn are linked to disciplines such as information technology, robotics, and bioengineering to enable the development of new or enhanced tools and devices to further basic scientific research, as well as lead to improvements in human health. Nanotechnology research takes advantage of the phenomenon that the properties of some materials change significantly at very small scales, often with surprisingly useful consequences. NIH-supported nanotechnology research exploits this phenomenon in efforts to develop devices with unique features for diagnosing and treating disease. It is a highly multidisciplinary field, drawing from disciplines such as applied physics, materials science, supramolecular chemistry, and mechanical and electrical engineering.

Many of the core challenges in research today require technologies, databases, and other scientific resources that are more sensitive, robust, and easily adaptable to unique applications than what currently exists. New technologies are needed, for example, to develop a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation; to develop a more precise knowledge of the combined effects of environmental exposures, individual susceptibility, and molecular events at the onset of disease; and to capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology. Moreover, widespread access to such tools will be essential for moving these fields forward.

The development, deployment, and use of biomedical information systems (i.e., disease registries and other databases) are essential to managing large amounts of data for research, clinical care, and public health—often referred to as "big data." Increasingly, these technologies serve not only as repositories of information but also as research tools in and of themselves, extending and, in some cases, augmenting the laboratory. For example, scientists are able to use molecular databases to study the profiles of individual tumors and conceptualize small-molecule anticancer agents to target them. However, new analytical tools are needed to harness large datasets to address increasingly complex questions, such as how the expression patterns of multiple genes are associated with a particular trait or response. Tools such as this are most effective when these databases are interoperable and capable of communicating with each other and making use of similar software applications. NIH also is attuned keenly to the importance and challenges associated with preserving, protecting, and ensuring the validity and security of information stored in biomedical databases.

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

NIH-supported efforts are affecting how health care providers, patients, and researchers will use information technology in the future. One such endeavor allows patients to access their own health information. Complete access to diagnostic results and treatment details will permit patients to play an active role in their own health care decision-making by asking more informed questions about their care. Patients will be able to provide this information to any health care provider regardless of their location. NIH supports research to ensure that the data are secure during storage and transmission and to address compliance with the Health Insurance Portability and Accountability Act (HIPAA). Benefits of this approach include a reduction in medical errors and elimination of duplicative diagnostic procedures.

Next-generation health care will offer consumers ultrasensitive technologies and techniques to assess normal and diseased states of the body, coupled with quick access to vast amounts of health-related data. New modes of collecting patient information, such as the Patient-Reported Outcomes Measurement Information System (PROMIS),[209] may improve how patients provide information on their conditions and how doctors use that information in

[209] http://www.nihpromis.org.

treatment decisions. An online computer-adaptive testing system, PROMIS records patient reports of symptoms related to a wide variety of chronic diseases and conditions such as pain, fatigue, and emotional distress.

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support its mission. NIH databases and information systems, particularly the more than 200 resources from NLM, have become indispensable national and international resources for biomedical research and public health. Several trans-NIH activities, including the recently launched BD2K initiative (more details below), feature the development of significant biomedical information resources, including the tools, infrastructure, and associated research needed to make databases and registries more valuable.

NIH efforts to develop and deploy disease registries, databases, and biomedical information systems to advance biomedical science, health, and health care focus on:

- *Scientific databases.* These databases archive and provide access to authoritative scientific literature, essential research data (including disease-specific data), and clinical research information.
- *Genomic information systems.* These information resources support genetics research and include storage of genetic data in registries, as well as analysis of this data.
- *Disease registries and surveillance systems.* NIH works with other federal and private entities to integrate disease registries for national and local use.

Examples of NIH's efforts in these three domains are outlined in the sections below. Additionally, to comply with Section 403 (a)(4)(C)(ii) of the Public Health Service Act to provide catalogs of disease registries and other data systems, Appendix G is included with an inventory of NIH intramural and extramural activities ongoing in FY 2012 and FY 2013 to develop or maintain databases, disease registries, and other information resources for the benefit of the larger research community. In 2013, NIH also launched a publicly accessible listing of NIH-supported data-sharing repositories that collect biomedical research data and make it accessible for reuse.[210]

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

- *Standardized vocabularies and data protocols.* NIH leads the government's efforts to develop standardized vocabularies and terminology to support interoperability among biomedical information systems in research and clinical settings. NLM is designated as the central coordinating body for clinical terminology standards within HHS.
- *Large-scale informatics infrastructure.* NIH funds the development of large-scale systems and tools that allow communities of researchers to collect, share, and analyze data needed for research, clinical care (including electronic health records), and public health.
- *Biomedical informatics research and training.* NIH is the largest federal funder of biomedical informatics research, which aims to advance the applications of computing to biomedicine for both research and clinical care. NLM supports research in biomedical informatics and training for informatics researchers and information specialists.

NIH Scientific Databases: Enhancing Access to Research Information

Keeping pace with the expanding volume of biomedical knowledge is a continuing challenge for scientists, clinicians, policy-makers, and the public; thus, NIH devotes considerable attention and resources to developing, expanding, and maintaining tools and resources for information management. Biomedical databases store and provide access to a wide range of information, including the results of scientific or clinical research studies, genomic information, standard reference materials (such as genome sequences or anatomical images), and published journal articles and citations of medical literature. Biomedical researchers, as well as a growing number of clinicians, public health officials, and consumers, widely use these databases. NIH often undertakes special initiatives to make these resources more accessible to a broader, more diverse set of users.

Among the most widely used of NIH's databases are those that collect and provide access to scientific literature. These comprehensive resources, developed and maintained

[210] http://www.nlm.nih.gov/NIHbmic/nih_data_sharing_repositories.html.

by NLM, are used extensively by scientists, health care providers, and consumers who seek trusted, peer-reviewed information on biomedical and health topics of interest. NIH houses the leading source of authoritative biomedical literature for professional and lay audiences. The exhaustive PubMed/MEDLINE database comprises more than 24 million citations for biomedical literature from MEDLINE, life science journals, and online books.

In addition, NIH continues to expand PubMed Central (PMC),[211] its digital archive of full-text scientific journal articles. PMC was established to provide online access to a growing number of scientific journal articles deposited by publishers and NIH-funded researchers, and it now provides public access to more than 3.2 million research articles. Some of this increase is attributable to an expanding scope of users—not only biomedical researchers but also clinicians, other practitioners, and consumers—that highlights the importance of this type of resource. In recognition of the fact that more people are accessing PMC from mobile devices, in 2012, NIH launched a new presentation format (called PubReader) that optimizes reading of articles from such devices.

PMC serves as the repository for manuscripts submitted in accordance with the NIH Public Access Policy, which ensures that the public and the scientific community have access to the published results of NIH-funded research by requiring NIH-funded scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to PMC. PMC software also is used by funding agencies in other countries to establish repositories for their funded research.

NIH also puts effort into developing and maintaining information systems that collect data stemming from biomedical research. These systems organize data and make it accessible for subsequent research. The PubChem database,[212] for example, houses the voluminous data on molecular structures and functions that is submitted from more than 280 organizations. It provides information about the biological activity of small molecules, organized as three linked databases along with a chemical structure similarity search tool. As of the end of 2013, PubChem contains data on more than 45 million distinct compounds and results from more than 1 million bioassays. PubChem, developed and maintained by NLM, is integrated with NLM's Entrez suite of biomedical information resources, which is a collection of some 40 databases of molecular and genomic data and biomedical literature. This integration enables users to retrieve related data from multiple databases and navigate among them with relative ease.

Recognizing that "a picture is worth a thousand words," toward the end of FY 2012 NLM launched Openi,[213] a system that enables the scientific community and the general public to search for visual information (clinical images, graphs, charts, diagrams and other illustrations) across 700,000 articles and 2.3 million figures from the open-access medical literature.

Individual ICs also support efforts to integrate the enormous data streams for the benefit of catalyzing research in certain diseases and disorders. For example, NIDCR supports the national FaceBase Consortium,[214] which has a goal of fostering a better understanding of the genetic instructions controlling development of the middle region of the human face by providing the research community with comprehensive and integrated datasets that include genetic and genomic data, gene expression pattern information, and human facial imagery. FOAs for new FaceBase individual science projects and the re-competition of the FaceBase data integration and management hub were released in FY 2013. To encourage the use of FaceBase data and resources, NIDCR supports small grants that focus on new approaches using existing FaceBase data and novel methods to analyze and integrate data to advance craniofacial research.[215]

In addition, NIA, in collaboration with the Alzheimer's Association, has developed the International Alzheimer's Disease Research Portfolio (IADRP),[216] a new, publicly available database to capture the full spectrum of current Alzheimer's disease research investments and resources, both in the U.S. and abroad. The IADRP enables public and private funders of Alzheimer's research to coordinate research planning, leverage resources, avoid duplication of funding efforts, and identify new opportunities in promising areas of growth. Along with NIA, more than 20 NIH ICs, 11 other federal agencies, and 6 nonfederal entities

[211] http://www.ncbi.nlm.nih.gov/pmc/.
[212] https://pubchem.ncbi.nlm.nih.gov/.
[213] http://openi.nlm.nih.gov/.
[214] https://www.facebase.org/.
[215] http://grants.nih.gov/grants/guide/pa-files/PAR-13-178.html.
[216] http://iadrp.nia.nih.gov/.

contribute to the database. Fourteen international research organizations—including ones from the U.K., Canada, Australia, and Poland—also have joined the collaboration.

The Dietary Supplement Label Database (DSLD)[217] is a joint project of ODS and NLM, developed in collaboration with the U.S. Department of Agriculture (USDA), CDC, FDA, and DoD. DSLD was launched in June 2013 as a searchable database for the information on the labels of dietary supplements in the U.S. marketplace. Users can search the database to identify supplements by label photograph, brand name, ingredients, and health-related claims. Approximately 1,000 new labels are entered into the DSLD each month, so eventually virtually all of the more than 55,000 dietary supplements in the U.S. marketplace will be included.

Genomic Information Systems: Understanding the Genetic Basis of Disease

NIH has made great strides in developing information resources to support genetics research. For example, GenBank,[218] the NIH genetic sequence database, is an annotated collection of all publically available DNA sequences. It is designed to provide access for the scientific community to the most up-to-date and comprehensive DNA sequence information. Considerable effort also has been aimed at supporting the analysis of data from GWAS, which explore the connection between common variants of specific genes (genotype information) and observable diseases or conditions (phenotype information, such as diabetes, high blood pressure, or obesity). NIH's dbGaP,[219] developed and operated by NLM, houses data from a number of GWAS, including those funded by NIH. NIH's GWAS Policy[220] encourages NIH grantees to submit their GWAS data to dbGaP and establishes procedures for making it available to other researchers to speed up disease gene discovery while at the same time protecting the privacy of research subjects in genomics studies.

In addition, several NIH ICs have established genetics repositories to accelerate research and multidisciplinary collaborations in specific disease areas. Programs such as the NEI eyeGENE,[221] the NIMH Repository and Genomics Resource,[222] the NIDA Center for Genetic Studies,[223] the NINDS Human Genetics Repository, the NIEHS Chemical Effects in Biological Systems Knowledge Base, and the NIA Genetics of Alzheimer's Disease Data Storage Site[224] give researchers access to vast storehouses of genetic and genomic data, DNA samples, and clinical data, along with informatics tools designed to facilitate their analyses. The wide availability of information linking genotype to phenotype should help researchers better understand gene-based diseases and speed development of effective therapies.

Disease Registries and Surveillance Systems: Tracking and Monitoring Disease

Disease registries and other surveillance systems collect information about the occurrence of specific diseases, such as cancer and Parkinson's disease, the kinds of treatment that patients receive, outcomes, and other information that might be relevant to researchers or public health officials. Increasingly, disease registries also include genomic data from registered patients. Registry information can therefore help identify causal factors of disease, assess the effectiveness of various interventions, and identify questions of concern to researchers, clinical professionals, and policy-makers.

For example, NCI's Surveillance, Epidemiology, and End Results (SEER) program[225] collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28 percent of the U.S. population, making it an authoritative source of information on cancer incidence and survival in the U.S. SEER has proven a formidable research resource and has been the foundation for innumerable studies, including recent research tying oral cancer risk to HPV among those younger than 45.[226]

Disease registries have been employed for research on autoimmune disorders, including Sjögren's syndrome, one of the most prevalent. A lack of data and biospecimens

[217] http://www.dsld.nlm.nih.gov/dsld/.
[218] http://www.ncbi.nlm.nih.gov/genbank/.
[219] http://www.ncbi.nlm.nih.gov/gap.
[220] On August 27, 2014, NIH issued the NIH Genomic Data Sharing Policy (GDS Policy). The GDS Policy is an extension of and replaces the GWAS data sharing policy. For more information, see http://gds.nih.gov/03policy2.html.
[221] https://www.nei.nih.gov/eyegene.
[222] https://www.nimhgenetics.org/.
[223] http://www.drugabuse.gov/researchers/research-resources/genetics-research-resources/nida-genetics-study-center-biorepository.
[224] https://www.niagads.org/.
[225] http://seer.cancer.gov/.
[226] Gayar OH, et al. *Otolaryngol Head Neck Surg.* 2014;150(4):594-601. PMID: 24452304.

available for research pose significant roadblocks to advancing discoveries in Sjögren's syndrome. Recognizing the problem, NIH spearheaded an effort to establish patient registries at two extramural institutions, as well as within its own intramural program. These groups work together to generate and share genome-wide genotyping data and clinical information from the cohorts enrolled.

Registries also provide a valuable source of information for tracking the effectiveness of particular treatments or interventions. The Interagency Registry for Mechanically Assisted Circulatory Support,[227] for example, is a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. NIH, FDA, and the Centers for Medicare & Medicaid Services (CMS) jointly support the registry. Use of standardized terminologies helps ensure that the data collected will facilitate improved patient evaluation and management while aiding in better device development.

Standardized Vocabularies, Data Protocols, and Tools

NIH continues to invest in tools that can increase the utility of its scientific databases and medical information sources. A key component of such efforts relates to the development and maintenance of standards and vocabularies for use in information systems used for research and clinical care, including electronic health records.[228] Standard vocabularies and ontologies (models of the relationships between concepts) improve information search, retrieval, and exchange by endowing systems with the ability to automatically perceive and retrieve information about related terms. As expansion of scientific frontiers produces new concepts, terms, and relationships, standard vocabularies must be regularly revised so that articles and other data can be properly indexed and search engines can find relevant and related terms.

As the central coordinating organization for vocabulary standards within HHS, NLM continues to update the Unified Medical Language System (UMLS),[229] which is used heavily in advanced biomedical research and data mining worldwide. The UMLS Metathesaurus,[230] with more than 11.6 million concept names from more than 150 source vocabularies, is a distribution mechanism for standard code sets and vocabularies used in health data systems. Many institutions apply UMLS resources in a wide variety of applications including information retrieval, natural language processing, creation of patient and research data, and the development of enterprise-wide vocabulary services for electronic health records.

NLM also produces and maintains a growing number of convenient vocabulary subsets to help electronic health record developers and users transition to use vocabulary standards, including subsets of frequently encountered patient problems, frequently ordered tests, and medications currently available in the U.S. market. In FY 2013, NLM released a new Value Set Authority Center[231] in collaboration with the Office of the National Coordinator for Health Information Technology, CMS, the HHS Office of the Secretary, and others to provide authoritative access to the standard vocabulary components of clinical quality measures.

Various ICs also spearhead efforts to develop standard vocabularies. For example, NIEHS has launched an initiative to develop a framework for environmental health science vocabulary to aid in data sharing, integration, and analysis.

Data harmonization efforts can similarly boost the impact of individual research by promoting the use of common measures across studies within and across particular research fields. By using common measures, researchers can more easily compare and combine datasets to detect more subtle and complex associations among variables, thereby promoting greater collaboration, efficiency, and return on investment. For example, in 2006, NHGRI initiated the PhenX Toolkit to provide standard measures related to complex diseases, phenotypic traits, and environmental exposures. Use of PhenX measures facilitates combining data from a variety of studies and makes it easier for investigators to expand a study design beyond the primary

[227] http://www.uab.edu/medicine/intermacs/.
[228] http://www.nlm.nih.gov/healthit/meaningful_use.html.
[229] http://www.nlm.nih.gov/research/umls/.
[230] http://www.nlm.nih.gov/pubs/factsheets/umlsmeta.html.
[231] https://vsac.nlm.nih.gov/.

research focus. Another example, supported by NINDS, is the Parkinson's Disease Biomarkers Program Data Management Resource,[232] which is designed to be used broadly to facilitate clinical research on Parkinson's disease by using a set of standardized data elements that will improve data quality, simplify data sharing, and promote meta-analyses and cross-study comparisons. This data management resource was the 2014 overall winner of the *Excellence.gov Awards* for innovative government information technology programs.[233] A number of other NIH ICs have launched projects to encourage the use of common data elements in funded research. In FY 2013, NIH's Biomedical Informatics Coordinating Committee established a trans-NIH working group to improve coordination, consistency, and communication of such efforts across ICs. In 2013, the working group launched a Common Data Element Resource Portal to provide integrated access to information about NIH's common data elements.[234]

Another example of the development of standardized tools designed to provide common measures for comparison across different diseases is PROMIS (mentioned earlier in this section). Patient-centered outcomes (PCOs) such as patient-reported outcomes are key to understanding how diseases, conditions, and their treatments influence patients' symptoms, functioning, and quality of life. Most PCO instruments have traditionally been used for disease-specific assessments rather than to facilitate within- or across-disease comparisons. The Common Fund supported the development of PROMIS,[203] which is creating new paradigms for how clinical information is collected, used, and reported. A rigorously tested patient-reported outcome measurement tool, PROMIS uses recent advances in information technology; psychometrics; and qualitative, cognitive, and health survey research to measure patient experiences that have a major impact on quality-of-life across a variety of chronic diseases. PROMIS tools measure what patients are able to do and how they feel by asking questions, and the tools provide a highly reliable and precise measure of patient-reported health status for physical, mental, and social well-being. PROMIS is unique in that measures have been standardized to cover different conditions, which allows comparison across diseases. Although originally designed as a research tool, PROMIS is receiving considerable support from health care providers who are interested in using it in their practices.

NIH supports a cloud-based library of tools for analyzing brain images and related data. The Neuroimaging Tools and Resources Clearinghouse (NITRC)[235] offers researchers cloud-based computing, which brings expanded research capabilities to both large- and small-scale researchers while reducing the costs of working with increasingly larger datasets. NITRC is a one-stop shop for software tools, data, and other resources for functional and structural neuroimaging analysis. Data available on NITRC includes brain images from MRI, PET, magnetoencephalography (MEG), and other types of brain scans. The 3D Brain Atlas Reconstructor, a software package for reconstructing 3-D models of brain structures, is one of the many software tools available from the library.

NCI supports The Cancer Imaging Archive,[236] which provides curated, de-identified, purpose-built collections of cancer patient medical images that are used by bioinformaticians to develop and apply radiomics tools for computer-aided interpretation of a variety of cancers. These collections have been used to mount "challenge contests" where individual researchers attack a specific problem in imaging (for example, rapidly and automatically determining the volume of a tumor), and the solutions are compared to determine the best approach.

The NCI Center for Biomedical Informatics and Information Technology (CBIIT)[237] provides IT infrastructure and informatics services in support of intramural research, grants management, and program administration. CBIIT also delivers resources to the cancer informatics community, including open-source software, collaboration tools, data collections, standardized vocabularies, metadata resources, and infrastructure. CBIIT administers the National Cancer Informatics Program (NCIP).[238] Launched in 2012, NCIP promotes the principles of open source, open data, and open science and cultivates collaborations within and beyond NCI to advance research across the continuum

[232] https://pdbp.ninds.nih.gov/.
[233] https://www.actiac.org/2014-excellencegov-award-winners-finalists.
[234] http://cde.nih.gov.
[235] http://www.nitrc.org/include/about_us.php.
[236] http://imaging.cancer.gov/informatics/thecancerimagingarchive.
[237] https://cbiit.nci.nih.gov/.
[238] https://cbiit.nci.nih.gov/ncip.

from basic discovery to clinical application. To facilitate collaboration among cancer researchers, CBIIT has established the NCIP Hub,[239] which allows groups to share a variety of resources including data, tools, publications, and training materials, as well as extended discussions of topics related to cancer informatics.

Large-Scale Informatics Infrastructure

In this age of big data, NIH also has embarked on a number of large-scale initiatives to develop and deploy infrastructure and tools for storing, sharing, integrating, and analyzing the large volumes of data routinely generated in research laboratories and in clinical settings. These initiatives tend to produce not only storehouses for data generated by research but also larger-scale networks for sharing data, linking researchers, and conducting further research. NIH supports a number of clinical research networks, which allows for standardized data reporting and sharing of information across clinical studies.

Launched in 2012, the NIH BD2K initiative[240] is the focal point for NIH's big data effort, and the initiative has the goal of enabling biomedical scientists to capitalize more fully on the big data being generated by research communities. With advances in technologies, these investigators are increasingly generating and using large, complex, and diverse datasets. Consequently, the biomedical research enterprise is increasingly becoming data intensive and data driven. However, the ability of researchers to locate, analyze, and use big data (and more generally all biomedical and behavioral data) is often limited for reasons related to access to relevant software and tools, expertise, and other factors. BD2K aims to develop the new approaches, standards, methods, tools, software, and competencies that will enhance the use of biomedical data by supporting research, implementation, and training in data science and other relevant fields. In July 2013, NIH announced that it will fund up to $24 million per year for four years to establish six to eight investigator-initiated Big Data to Knowledge Centers of Excellence.[241]

To address challenges posed by the enormous volumes of data routinely generated by high-throughput research technologies, the NCI CBIIT is working in close collaboration with the Center for Cancer Genomics to launch a set of Cancer Genomics Cloud Pilots[242] where, initially, data from TCGA and analysis tools will be co-located with computing resources, with access democratized across the widest possible audience to accelerate cancer research.

To support and accelerate research in the prevention, cause, diagnosis, and treatment of research on autism spectrum disorders (ASDs), NIH created the National Database for Autism Research (NDAR).[243] This database collects a wide range of data types, including phenotypic, clinical, and genomic, as well as de-identified medical images—all derived from individuals who participate in ASD research, regardless of the source of funding. NDAR provides the infrastructure to store, search across, retrieve, and analyze these varied types of data. At NIH, approximately 80 percent of all ongoing ASD grants involving human participants have data sharing with NDAR as a condition of their awards; by 2015, virtually all such NIH ASD research is expected to include these terms. NDAR also coordinates data access with other federal databases, such as the NIH Pediatric MRI Data Repository,[244] as well as several private databases, such as the Autism Genetics Resource Exchange. NDAR provides an example of how NIH is poised to take full advantage of the big data revolution through efforts to promote common data elements in neuroscience research and broad data sharing.

Another ambitious informatics effort, the Human Connectome Project, is using new, high-resolution imaging methods to provide the first detailed "wiring diagram" of the living human brain.[245] In one of the first reports from this project, scientists discovered a surprisingly simple 3-D organization of fiber tracts in the human brain.[246] A five-year project that began in 2010, the Human Connectome Project has posted extensive imaging results and cognitive data on a reference cohort of 68 healthy volunteers on its way to a database of 1,200 participants, including 300 pairs of twins.

[239] https://nciphub.org/.
[240] https://datascience.nih.gov/bd2k.
[241] http://www.nih.gov/news/health/jul2013/nih-22.htm.
[242] https://cbiit.nci.nih.gov/ncip/nci-cancer-genomics-cloud-pilots.
[243] http://ndar.nih.gov.
[244] http://pediatricmri.nih.gov/nihpd/info/index.html.
[245] https://neurosciencebluprint.nih.gov/connectome/.
[246] Wedeen VJ, et al. *Science* 2012;335(6076):1628-34. PMID: 22461612.

Other efforts aim to provide the informatics infrastructure include the CardioVascular Research Grid,[247] which provides infrastructure for sharing cardiovascular data and data analysis tools. Another example is the National Centers for Biomedical Computing.[248] A Common Fund initiative, these Centers are intended to be part of the national infrastructure in biomedical informatics and computational biology, creating innovative software programs and other tools that enable the biomedical community to integrate, analyze, model, simulate, and share data on human health and disease.

Biomedical Informatics Research and Training

Ensuring continued advances in biomedical informatics resources requires active support of fundamental research that seeds the further development of new tools, resources, and approaches. It is also critical to generate a continuous supply of skilled biomedical informatics researchers, information specialists (such as medical librarians), and life sciences researchers trained in bioinformatics. NIH continues to expand its efforts in bioinformatics research and training in response to the growing importance of informatics in the biomedical and life sciences. NIH also is the principal source of support for research training in biomedical informatics, with NLM providing research training grants to 14 institutions that enroll approximately 200 predoctoral and postdoctoral trainees each year.

Mobile Health and Point-of-Care Technologies

Ideally, patients would have access to high-quality and consistent health care regardless of where they live. Realizing this vision necessitates the development of portable, reliable, and inexpensive equipment to diagnose and treat patients. To achieve this also will require the leveraging of technologies developed in other fields, such as telecommunications. Advances in fiber-optic and wireless communications devices allow physicians to engage in telemedicine (the transmission via the Internet of medical information) to deliver health care by communicating with other physicians or pathologists thousands of miles away.

NIBIB currently funds the Point-of-Care Technologies Research Network (POCTRN),[249] a network of three centers that are establishing new point-of-care technologies at various stages of development. The Center for Future Technologies in Cancer Care focuses on the identification, prototyping, and early clinical assessment of innovative point-of-care technologies for the treatment, screening, diagnosis, and monitoring of cancers. The Center for Point-of-Care Tests for Sexually Transmitted Diseases creates and tests unique methods for the diagnosis of sexually transmitted diseases, including the home delivery of over-the-counter tests to end users via the Internet. The POCTRN Center in Primary Care serves as a national leader in transforming point-of-care technologies into commercially viable, clinically focused solutions for improving primary health care. The network emphasizes collaboration between front-line health care workers and technology developers so appropriate tools are created to meet clinical needs.

The demands of primary care providers are becoming increasingly complex as the population ages and the burden of chronic disease grows. Emerging microfluidic, nanotechnology, and sensor miniaturization technologies are making it possible to develop a new generation of point-of-care test systems designed to improve the efficiencies of primary care practices. This focus aims to shift clinical laboratory testing to the primary care office, home, and bedside. Currently, most tests need to be sent to a laboratory, and results may not be available for several days. This time lag poses a burden on providers and patients and delays treatment. Point-of-care diagnostic technologies that are in various stages of development include a home screening test for sexually transmitted diseases, a pre-screening tool for colorectal cancer, detection of lung cancer biomarkers, and identifying ear infections. Also, a NIBIB grantee developed a microfluidic device designed to diagnose tuberculosis (TB), which was recently tested with patients known to have TB and with healthy patients. The device accurately identified all those with TB.[250] Tests currently used can take weeks for results and may fail to diagnose up to 40 percent of those with the infection.

[247] http://cvrgrid.org/.
[248] http://www.ncibi.org/gateway/ncbcs.html.
[249] http://www.nibib.nih.gov/research/featured-programs/point-care-technologies-research-network.
[250] http://www.nibib.nih.gov/news-events/newsroom/portable-device-provides-rapid-accurate-diagnosis-tuberculosis-other-bacterial.

Figure 2-12. *Fogarty International Center has launched a new program to advance mHealth research. Credit: David Snyder, courtesy of FIC.*

Point-of-care devices allow diagnosis, monitoring, and treatment to be more efficient and practical for patients and physicians, in part due to technological advances that have vastly broadened their application. NIBIB supports development of these technologies that are noninvasive or minimally invasive, such as a handheld device that uses lasers and sound waves to detect the depth of skin cancer. Accurately measuring how deep a melanoma tumor extends into the skin can help in the diagnosis and treatment of this type of cancer, which is increasingly common. The device uses photoacoustic microscopy to measure tumors beneath the skin, which in some cases may eliminate the need for biopsy.

Likewise, methods that take hours and require precise conditions for processing tissue samples limit when and where tests can be conducted. By taking advantage of digital or single-molecule quantitative assays, researchers have found a way to use a "lab on a chip" device and a cellphone to calculate a precise concentration of molecules from a sample.[251] With the "SlipChip" device, no electricity is needed, a huge advantage over the current polymerase chain reaction (PCR) methods. The new method also works in environments where temperature, light, and humidity cannot be controlled. This method splits a sample into

[251] Shen F, et al. *J Am Chem Soc.* 2011;133(44):17705-12. PMID: 21995644.

amounts so small that they only contain one or no target molecules and deposits the small amounts into wells on the chip. A new process for amplification of the samples produces a bright fluorescent signal if a target molecule is present. This gives a positive (yes, molecule is present) or negative (no, molecule is not present) result. The concentration or qualitative result is calculated from the number of wells in the "SlipChip" with a positive result. NIBIB support for this type of research can lead to faster and earlier diagnosis and better health outcomes.

The term *mobile health* (mHealth) refers to the use of mobile devices in the service of health care or public health. NIH has an interest in the development and use of mobile technologies to rapidly collect, assess, and use health data to improve the quality of care. FIC supports an mHealth research program that encourages multidisciplinary teams to develop, adapt, optimize, and evaluate mHealth tools or interventions to prevent, diagnose, manage, and treat health conditions primarily in low- and middle-income countries, with the potential for use in low resource or underserved settings in the U.S. In addition, research into technology that does not require electricity offers a key advantage for point-of-care technologies to be utilized in remote areas. A DNA amplification device that does not require electricity or a battery pack to detect HIV in the early stages of infection so treatment and preventive measures can begin immediately is under development.[252] This technology could be exploited in other molecular diagnostic detection methods for bacteria such as *Salmonella enterica* in agricultural settings.

NIDCR supports initiatives that couple discoveries in the pathophysiology of human diseases with innovations in engineering and electronics to develop point-of-care medical diagnostic devices. For example, NIDCR supports research to use saliva in a small, all-in-one device to rapidly measure biomarkers associated with disease allowing early detection, whether in a clinic or in remote resource-poor settings. Already in progress is an NIDCR-supported research project that yielded a miniaturized, portable nanobiochip that uses nanoliter volumes of saliva to identify biomarkers for a multitude of diagnostic purposes.[253] During the first phase of this project, researchers found promising predictive markers for cardiac events; the validation of these markers is ongoing. This is a first step toward developing effective and personalized disease-management strategies.

These mobile technologies provide exceptional opportunities to measure behaviors and environmental influences objectively, precisely, and in real time and to deliver automated and adaptive behavioral interventions. Therefore, OBSSR sponsors a training institute on mHealth that pairs behavioral and biomedical scientists with engineering and computer scientists to leverage these technologies to better measure and change behavior.

Visualizing Biological Systems

Better tools and techniques to understand activities within cells, tissues, and organ systems enable researchers to probe deeper to gain an understanding of the biological systems and networks that control both normal function and diseased states. For example, two NIH intramural research groups are collaborating to develop a next-generation MRI system to examine the human brain. The system uses a 7-tesla magnet to produce highly detailed images that reveal structures not visible using conventional MRI.

Recent advances in imaging technology also present opportunities to advance quantitative imaging and the use of imaging biomarkers in clinical trials and clinical practice. NIBIB has funded more than 20 projects within a public-private consortium called the Quantitative Imaging Biomarkers Alliance (QIBA),[254] which aims to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time. QIBA has selected several imaging biomarker candidates and has made advances in establishing standards, methods, and processes aimed at accelerating translation of these biomarkers from bench to bedside by engaging researchers, health care professionals, and industry. The NIA-supported Alzheimer's Disease Neuroimaging Initiative[255] also has been successful in identifying imaging and fluid biomarkers for the disease, which facilitated the first revision in 27 years of the clinical diagnostic criteria for Alzheimer's. The updated criteria offer a new paradigm for Alzheimer's, covering the disease as it gradually progresses over many years, from its earliest preclinical, pre-symptomatic phase through

[252] Singleton J, et al. *Proc SPIE.* 2013;8615:86150R. PMID: 25426269.
[253] Miller CS, et al. *Biomark Med.* 2010;4:171-189. PMID: 20387312.
[254] https://www.rsna.org/QIBA/.
[255] http://www.adni-info.org/.

mild cognitive impairment to advanced dementia. The new guidelines also address the use of imaging and biomarkers to determine whether changes in the brain and body fluids are due to the disease.

From single cells to entire organs, NIBIB supports research that can better visualize and monitor changes in order to understand, diagnose, and treat disease. For example, a tool to track organ structure and function is currently under development by one NIBIB grantee, who is developing a method to follow kidney function that will enable early screening of toxicity and malformations. The grantee obtained high-resolution 4-D images of kidneys in normal mice and measured structural/functional changes in the kidney over a developmental period of 17 weeks.[256] The enhanced data from this technique can be used to study normal kidney development and function, as well as diseases of the kidney that require early detection and intervention.

NIBIB also supports efforts to reduce radiation dose in imaging. Several approaches are underway, including improving technologies that reduce imaging time or reduce dosage levels in scans such as CT while maintaining image quality.

In addition to new imaging technology, other innovative visualization techniques also are helping us to understand the brain at the most fundamental level. With funding from NIMH and the NIH Director's Transformative Research Award Program, researchers have enabled us to study the brain's finer workings while preserving its 3-D structure and the integrity of its circuitry and other biological machinery. Called CLARITY (Clear Lipid-exchanged Anatomically Rigid Imaging/immunostaining-compatible Tissue hYdrogel), this technology replaces the fat that normally holds the brain's working components in place with a permeable hydrogel, allowing researchers to make the brain's normally opaque and impenetrable tissue transparent and permeable.[257] In addition to its use in animal research, this method can be used in postmortem human brains—even tissue that has been stored for years. Tools like CLARITY will shed light on how the brain works in health and illness.

[256] Xie L, et al. *NMR Biomed.* 2014;27(9):1094-102. PMID: 25066408.
[257] Chung K, et al. *Nature*. 2013;497(7449):332-7. PMID: 23575631.

Image-Guided Interventions

To detect disease in its earliest stages, and thereby preempt it before symptoms appear, clinicians will need to examine smaller, more localized areas of the body. Image-guided interventions (IGIs)—treatments or procedures that precisely target areas within the body with the aid of imaging techniques such as MRI, CT, or ultrasound—enable clinicians to look beneath the surface anatomy to visualize underlying pathology. As a result, images can be used to navigate the anatomy for biopsy and treatment of disease. In addition to diagnosing at-risk individuals, IGI may offer a safer, less-invasive, and often less-costly approach to many surgical procedures. Compared with traditional open surgery, minimally invasive procedures result in less tissue trauma, less scarring, and faster postoperative recovery time, which translates into shorter hospital stays and a more rapid return to family and work.

NIH's Center for Interventional Oncology[258] is leading the way in developing and disseminating innovative cost-effective alternatives to open surgery. Physicians can navigate through the body using "medical GPS"—real-time imaging such as MRI, CT, or ultrasound. This effort in collaboration with NCI intramural investigators resulted in commercialization of the technique (UroNav) in 2013, for improved diagnosis and treatment of prostate cancer. Once at the desired location, the physician can insert a needle into a tumor, deliver heat to destroy it, and then deposit a drug to eliminate residual cancer cells. The Center is also pioneering new image-guided approaches to track personalized responses to new drug therapies over time. These endeavors are contributing to the future of personalized medicine.

In both extramural grants and the NCI Experimental Therapeutics Program (NExT),[259] NCI is supporting molecularly targeted intra-operative imaging approaches to clearly delineate the margins of tumors so that surgeons can be confident of removing all of a tumor with as little normal tissue as possible.

NIBIB also is developing ways to surgically remove all the tumor tissue while sparing surrounding healthy tissue such as nerves. Nerves and their branches that extend through or near the parotid (salivary) and prostate glands

[258] http://clinicalcenter.nih.gov/centerio/index.html.
[259] http://next.cancer.gov/.

can be particularly challenging for surgeons to separate from tumors. One approach to overcome this challenge is progressing into animal studies. It involves using fluorescently labeled probes for imaging during surgery so surgeons can see where the nerves begin and end and can separate the tumor from critical nerve connections.[260, 261, 262] The technology also may be applicable to guiding the repair of peripheral nerves damaged by trauma.

The challenge of separating tumor and healthy tissue is particularly critical when removing brain gliomas because damage to surrounding healthy tissue can have severe consequences and a tumor may grow back if it is not completely removed. NIH supports development of image-guided systems to overcome these challenges and improve the precision of these difficult surgeries. In one approach, researchers use mass spectrometry to identify metabolites that are present in brain tumors but not in healthy tissue. During surgery, samples are removed and processed to measure the mass and charge of the metabolites. This approach allows surgeons to more precisely remove tumor tissue while sparing healthy tissue.[263]

Historically, MRI real-time guidance for minimally invasive procedures has been challenging because MRI scanners are designed such that, once a person is in the MRI scanner, the body part of interest is not easily accessible to someone performing a procedure. In addition, any equipment used in the procedure, such as surgical instruments and interventional devices, would need to be MRI compatible (i.e., non-magnetic). That being said, real-time MRI could provide extremely valuable information during certain minimally invasive procedures that are not furnished by other imaging modalities. For example, during catheter-based neuro-interventional procedures to open vessels after a stroke, MRI assessment of viable downstream brain tissue is critical information

[260] Gibbs SL, et al. *PLoS One.* 2013;8(9):e73493. PMID: 24039960.
[261] Cotero VE, et al. *Mol Imaging Biol.* 2012;14(6):708-17. PMID: 22488576.
[262] Bajaj A, et al. *J Histochem Cytochem.* 2013;61(1):19-30. PMID: 23092790.
[263] Santagata S, et al. *Proc Natl Acad Sci U S A*. 2014;111(30):11121-6. PMID: 24982150.

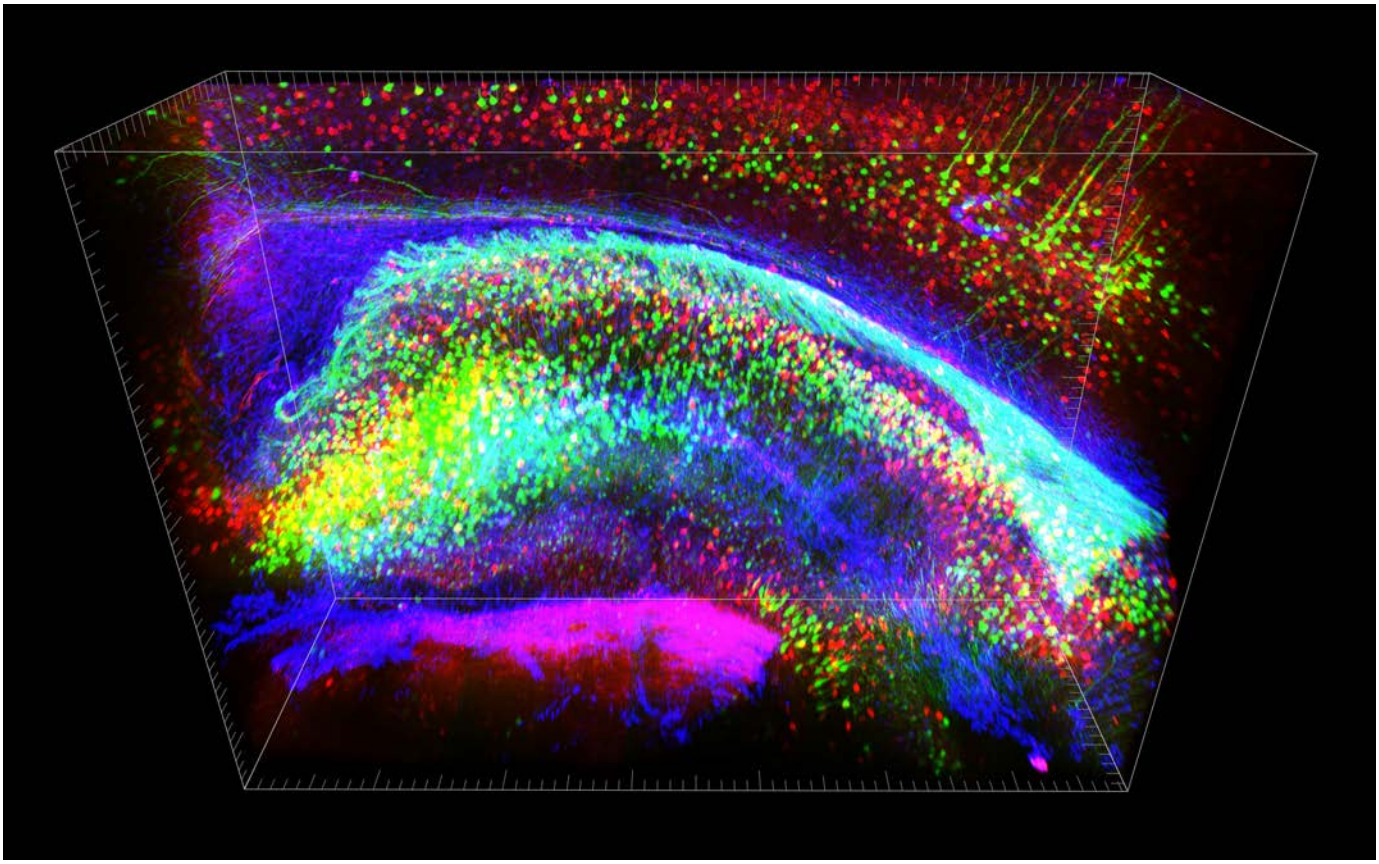


Figure 2-13. *CLARITY provided this 3-D view showing a thick slice of a mouse brain's memory hub, or hippocampus. It reveals a few different types of cells: projecting neurons (green), connecting interneurons (red), and layers of support cells, or glia (blue). Conventional 2-D methods require that brain tissue be thinly sliced, sacrificing the ability to analyze such intact components in relation to each other. Credit: Kwanghun Chung, Ph.D., and Karl Deisseroth, M.D., Ph.D., Stanford University.*

because unblocking a vessel supplying dead brain tissue is associated with an unacceptable risk of secondary hemorrhage. A remotely steerable MRI compatible catheter could be an important tool for interventional neuroradiologists and is under development.

Adding the benefits of robotics to image-guided interventions further expands the capabilities in this area.[264] Robotic tools can fit into tiny incisions and control tools remotely, allowing for more precision and, importantly, less fatigue for physicians performing these procedures. With NIBIB support, an image-guided device under development uses robotically controlled small needles that can be inserted into the brain through the nose to remove tumors. Investigators also are seeking to better understand relationships between surgical expertise, teamwork, and technology in robotic surgery to identify opportunities to improve performance, reduce errors, and shorten the learning curve for surgeons using this advanced technology.

Investments in Research Infrastructure

Advances in the development of new technology cannot come without supporting the infrastructure that undergirds the research endeavor. To that end, NIH supports a Shared Instrumentation Grant[265] and High-End Instrumentation Program, which provides new generation technologies to groups of NIH-supported extramural investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. NIH also continuously seeks to improve the current "state-of-the-art" in different technology areas.

Large-Scale Collaborative Activities

NIH creates critical, often unique technology and methods and applies them to a broad range of basic, translational, and clinical research through the Biomedical Technology Resources (BTRs), including Biomedical Technology Research Centers (BTRCs)[266] supported by NIBIB and Biomedical Technology Research Resources (BTRRs)[267] supported by NIGMS. There are currently 64 BTRs nationwide. These centers represent a critical mass of technological and intellectual resources with a strong focus on technology dissemination as well as service and training of investigators from bench to bedside. As a result, the BTRs annually enable research of more than 7,000 investigators that are funded by NIH and other agencies. Cutting-edge technologies and new tools developed by the BTRs that are available to research communities include biomedical imaging, microscopy, and spectrometry; computation, informatics, and modeling; artificial tissues/organs; drug delivery; bioelectronics and biomechanical devices; structural biology; proteomics; and glycomics. The BTRs also serve as catalysts for integrating the diverse efforts of NIH-supported researchers and providing technological infrastructure, experimental and computational resources, and necessary expertise.

One goal of BTRCs that support biomedical imaging research is the development of MRI technologies for increased signal sensitivity, higher image resolution, decreased acquisition time, and high-performance computer visualization and analysis software. Magnetic resonance image protocols with reduced acquisition time, developed by the Center for NMR Imaging and Localized Spectroscopy, have facilitated human studies in the Human Connectome Project. Recent developments in a technique called Chemical Exchange Saturation Transfer (CEST) MRI by the Center for Magnetic Resonance and Optical Imaging allows the detection of disrupted heart metabolism associated with damage of the heart, often a sign of heart disease, and the detection of abnormal brain metabolite and neurotransmitter associated with neurodegenerative diseases. This technique could help doctors identify signs of disease earlier via other methods. A similar technique developed by the Resource for Quantitative Functional MRI allows measurement of protein in the brain that can be used as imaging biomarkers for radiation necrosis after brain tumor irradiation. Also, the Laboratory of Neuro Imaging Resource, which plays an important role in the ADNI, develops and disseminates computational tools for neuroimaging and brain mapping to the research community.

[264] http://www.nibib.nih.gov/sites/default/files/Image-Guided%20Robotic%20Interventions%20Fact%20Sheet_0.pdf.
[265] https://dpcpsi.nih.gov/orip/diic/shared_instrumentation.
[266] http://www.nibib.nih.gov/research/featured-programs/biomedical-technology-resource-centers.
[267] http://publications.nigms.nih.gov/btrrs/searchresults.asp.

Funded by NIGMS, the Biomedical Informatics Research Network[268] is a virtual community of shared informatics resources. The network makes digital research data freely available for sharing and exchange among communities of researchers. Its data integration tools allow searching across distributed databases, and it provides tools for data analysis, management, and collaborative research. The resulting collaborative environment extends beyond the boundaries of individual laboratories to enable collaborations that cross geographic and disciplinary boundaries. Basic and clinical investigators are able to share disparate data as well as powerful new analytical tools and software across animal models and among multiple sites. This major initiative was developed to allow neuroimagers to share data and tools, but the infrastructure is generic and therefore applicable to other disciplines.

Bringing a Multitude of Scientific Disciplines Together

NIH fosters and cultivates cooperative research between health scientists and quantitative scientists so that fundamental discoveries and tools can be developed, even when their specific applications might not be obvious. For example, the laser, which was originally developed in physics laboratories studying energy and light, has been adapted for microscopes that are critical to many research areas as well as a variety of surgical tools, including systems for laser eye surgery.

Partnerships among engineers, clinicians, scientists, and industrial technologists provide a reservoir of information for NIH investigators. One such partnership is creating innovative technologies to assist combat veterans who have suffered limb damage or loss and civilian amputees and those with spinal cord injuries. A range of electronic and robotic devices will help these individuals stand and move. A new generation of hand and arm prostheses that provide fine finger movement and a sense of touch are especially promising.

NIH and NASA have a strong history of collaboration and share many interests in the life and health sciences. In 2012 and 2013, NIH staff co-chaired a Fast-Track Action Committee on the Utilization of the International Space

[268] http://www.birncommunity.org/.

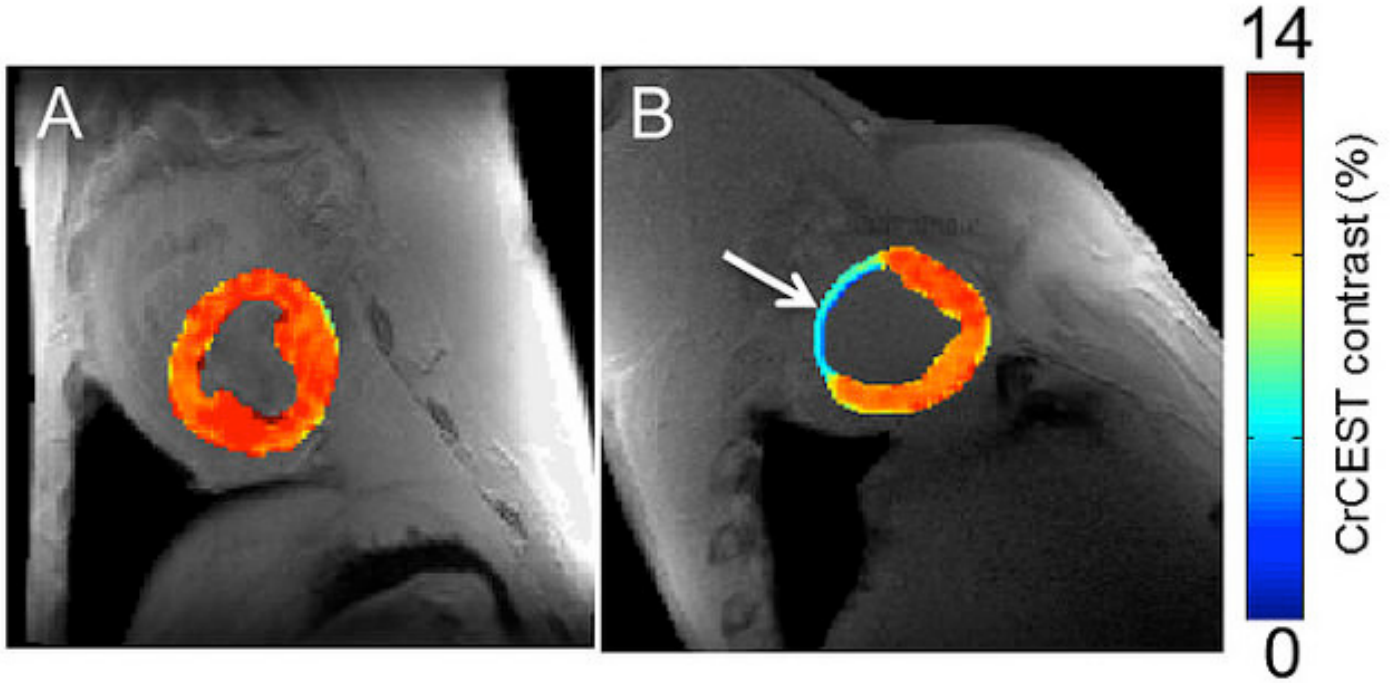


Figure 2-14. *Changes in creatine levels detected using Chemical Exchange Saturation Transfer MRI are mapped onto anatomical images of pig heart tissue. Panel B shows decreased creatine levels (blue) in an area that corresponds to tissue death, as indicated by the arrow. Credit: Adapted by permission from Macmillan Publishers Ltd:* Nature Medicine:20*(2), A technique for in vivo mapping of myocardial creatine kinase metabolism. Copyright 2014.*

Station (ISS) as a National Laboratory.[269] The Life Sciences Subcommittee of the National Science and Technology Council established the committee to address a range of issues and needs associated with developing a coordinated federal research agenda for the ISS National Laboratory. Representatives from USDA, the Department of Energy (DoE), NSF, and the National Institute of Standards and Technology also participated.

NIEHS is the designated lead for HHS to the U.S. Global Change Research Program,[270] which coordinates climate change efforts across 13 member agencies. NIEHS co-sponsors, with the National Oceanic and Atmospheric Administration and CDC, the program's Interagency Crosscutting Working Group on Climate Change and Human Health. Collaborative efforts of this group include a Metadata Access to Climate and Health Web portal that links metadata (data about data) sets from the climate science world with those from health agencies to facilitate cross-cutting research and contributions to development of the health chapter of the National Climate Assessment that identifies current and future climate change impacts in the U.S.

NIH, through the FIC-led Framework Programs for Global Health Innovation,[271] brings together scientists from different disciplines to develop innovative solutions for complex health problems in disadvantaged populations. This program fosters innovative, multidisciplinary solutions by requiring participation from at least three universities, departments, or entities of distinct disciplines, and participants are encouraged to form and consult with a consortium that can include external private, governmental, or nongovernmental organizations that can provide special expertise and experience. Recently, a partnership composed of microbiologists, engineers, architects, and public health researchers developed paper-based and clay water filters intended to prevent diarrheal diseases in children, HIV-positive adults, and others in a remote area of South Africa. Another partnership of trainees and scientists from engineering, architecture, and medicine are developing new upper-air disinfection technologies to prevent the spread of multiply and extremely resistant TB in crowded settings such as hospitals and shelters in sub-Saharan Africa while considering the design of buildings that will maximize the effectiveness of such technological interventions.

Nanotechnology

A sheet of paper is about 100,000 nanometers thick. The field of nanotechnology deals with matter approximately 1 to 100 nanometers in dimension. At these scales, matter exhibits unusual biological, chemical, and physical properties. By bringing together researchers from physics, materials science, and engineering, NIH is developing a powerful cadre of investigators who will use nanotechnology to significantly change ways to diagnose and treat diseases.

Sharing information across disciplines is critical to nanotechnology research. NCI's Alliance for Nanotechnology in Cancer brings together physical scientists and engineers working at the nano scale with cancer biologists and clinical oncologists to develop new devices and assays that will enable more effective cancer therapies and earlier diagnoses. The Alliance has built a community of researchers who not only work on new technologies but also actively share their knowledge with the larger medical community to inform and educate others about new, emerging opportunities of cancer nanotechnology. New nanodevices that quickly and accurately assess proteins, DNA, and RNA structures implicated in cancer; nanoparticle imaging agents to clearly visualize cancer; and implantable nanosystems to deliver drugs, monitor cancer progression, and assess therapeutic response will reshape the toolkit clinicians use to fight cancer.

NIEHS has established the Centers for Nanotechnology Health Implications Research, a consortium of eight academic institutions that are studying the potential health effects associated with exposure to engineered nanomaterials. The major focus of these centers is to understand how engineered nanomaterials interact at the molecular, cellular, organ, and animal levels to predict toxicity and design benign nanomaterials. Much of this funding in basic research has served to translate physicochemical-biological understandings into new nano-based interventions. In addition, the Common Fund's Regulatory Science program and FDA funded a

[269] http://www.whitehouse.gov/sites/default/files/microsites/ostp/NSTC/final_iss_report_2013.pdf.
[270] http://www.globalchange.gov/.
[271] http://www.fic.nih.gov/programs/pages/framework-innovations.aspx.

project to develop a new method to predict the potential harmful effects of nanoparticles intended for use in clinical applications prior to their testing in humans.[272]

Nanotechnology is opening doors into cell structures in unprecedented ways. A team of NIBIB-supported bioengineers has developed a DNA clamp that can detect mutations at the DNA level with greater efficiency than methods currently in use. This work could facilitate rapid screening of those diseases that have a genetic basis, such as cancer, and provide new tools for more advanced nanotechnology. The clamp is a nanoswitch that binds to a DNA target, after which the clamp closes and activates a fluorescent signal to indicate the presence of a mutation.[273]

A 3-D–printed hydrogel device that holds nanoparticles developed by nanoengineers has the ability to function much like the liver to remove toxins from the blood.[274] The device is used outside the body like dialysis and uses nanoparticles in a hydrogel matrix to trap the toxins, turning red to indicate that toxins have been trapped in the hydrogel. The technology developed to print the hydrogel device is a new biofabrication technology developed with NIBIB, NEI, and NINDS support.

Transforming Health Care

For more than 35 years, NIH has pioneered the development of neural interfaces, which connect the nervous system to internal or external devices. Neural interfaces include neural prosthetics to restore or supplement nervous system function lost through disease or injury. Early NIH research led directly to the development of cochlear implants for the hearing impaired, which are the most widely used neuroprostheses. According to FDA, as of December 2012, approximately 324,200 people worldwide have received implants.[275] Retinal implants for the visually impaired are in advanced development, and in February 2013, FDA approved the Argus II Retinal Prosthesis System, the first implanted device that allows patients with advanced retinitis pigmentosa (RP) to regain ambulatory vision. RP is a rare, untreatable degenerative eye disease that damages the retina. The device was developed by a small company, Second Sight, with support from NEI, DoE, and NSF.

Neural stimulators that provide therapy are another type of neural interface. Deep brain stimulation through implanted stimulators is now approved for treatment of essential tremor, Parkinson's disease, and dystonia and is in testing for several other brain disorders. A recently developed implanted device for people with epilepsy detects abnormal electrical activity in the brain and stimulates the brain to prevent seizures from fully developing.[276] Another type of neural interface, the Brain Computer Interface (BCI), enables people to control a computer or other device by signals recorded directly from their brain. For example, in an NIH-funded clinical trial, a surgically implanted BCI device enabled a paralyzed woman to control a robotic arm well enough to reach for and sip from a drink on her own for the first time in nearly 15 years.[277] Because the nervous system influences the function of all organ systems, neural interfaces that modulate nerve signals to the body's organs offer a potentially powerful way to treat many diseases, including hypertension, heart disease, gastrointestinal disorders, type 2 diabetes, and inflammatory disorders.

NIH is leading the way in the development of new technologies to provide disease diagnosis and treatment simultaneously. The concept of combining a therapeutic with a diagnostic agent is rapidly evolving and goes beyond traditional diagnostic tests that screen or confirm the presence of a disease. With specialized molecular imaging techniques and biomarkers, tailored and personalized medicine approaches could predict risks of disease, diagnose disease, and monitor therapeutic response, leading to real-time, cost-effective treatment.

[272] Pham CT, et al. *Nanomedicine.* 2014;10(3):651-60. PMID: 24211337.
[273] Idili A, et al. *ACS Nano.* 2013;7(12):10863-9. PMID: 24219761.
[274] Gou M, et al. *Nat Commun* 2014;5:3774. PMID: 24805923.
[275] http://www.nidcd.nih.gov/health/hearing/pages/coch.aspx.
[276] http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm376685.htm.
[277] Hochberg LR, et al. *Nature.* 2012;16:485(7398):372-5. PMID: 22596161.

Chapter 3: Research in Diseases, Disorders, and Health Conditions

Cancer

Although significant progress has been made in reducing the burden of cancer in the U.S., cancer remains a leading cause of death. According to CDC, in 2010, cancer maintained its long-standing place as the second leading cause of death in the U.S., surpassed only by heart disease.[278] In 2013, an estimated 580,350 people died of some form of cancer and an estimated 1,660,290 individuals were newly diagnosed with cancer.[279] Also in 2013, according to studies by NCI,[280] medical costs associated with cancer totaled $134.2 billion and are projected to reach at least $158 billion by 2020 (in 2010 dollars).[281] Although U.S. death rates for the most common cancers and for all cancers combined have decreased significantly since 1995, the annual number of cancer diagnoses is projected to rise to 2.1 million by 2025 because of the growth and aging of the population.

Cancer research funded and conducted by NIH is critical to the national and global effort to ameliorate and reduce the adverse effects of cancer on the health and lives of cancer patients, their families, and communities, as well as on the social and economic well-being of institutions, societies, and entire nations. Formidable challenges confront this effort. Cancer is not a single disease, but is a group of more than 100 diseases in which genetic changes disrupt cell function. Moreover, within each type of cancer, an individual's tumor can differ greatly due to complex biological factors. Cancer arises from alterations in the interactions among layered biological systems. The many different forms of cancer can be understood only by characterizing these systems and how they interact. NIH cancer research programs aim to improve our understanding of cancer as a multiscale, multidimensional disease system. This approach provides a context for research on:

- Identifying substances in our environment that we know or suspect will cause cancer
- Preventing cancer through use of risk assessments based on genetic susceptibilities and environmental exposures
- Detecting and diagnosing cancer based on knowledge of cancer-signaling pathways and biomarkers
- Predicting cancer progression and outcomes based on examination of the tumor microenvironment and interactions between tumor cells and surrounding, noncancerous cells in promoting metastasis, drug resistance, and tumor recurrence
- Developing targeted interventions for individual cancer patients based on the biology of their individual tumors and predictions of their response to treatment
- Addressing the unique needs of the growing number of cancer survivors

Precision medicine based on molecular characterization of individual cancers is the vision that provides the foundation for NIH's approach to cancer research and treatment. With the progressive realization of this vision, clinicians will have the ability to use detailed information about an individual's cancer and employ molecular and clinical data to guide the selection of therapies that are most likely to be safe and effective for that person. Precision medicine promises

[278] Murphy SL, et al. Table B. Deaths and death rates for 2010, and age-adjusted death rates and percent changes from 2009 to 2010, for the 15 leading causes of death: United States, final 2009 and preliminary 2010. *National Vital Statistics Reports*. 2012;60(4):31. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf.
[279] Siegel R, et al. *CA Cancer J Clin*. 2013;63(1):11–30. PMID: 23335087.
[280] http://cancercontrol.cancer.gov/index.html.
[281] http://costprojections.cancer.gov/.

Disclaimer: Links in this chapter were last accessed on 2/11/2016.

to improve quality of life for cancer survivors by minimizing adverse side effects of therapy and reducing disparities among populations currently experiencing an excess burden of cancer.

The Organization of Cancer Research at NIH

Although cancer research is conducted and supported by multiple ICs at NIH, NCI spearheads the Agency's efforts and programs along the continuum from basic to translational to clinical research. Five NCI extramural divisions support research at 650 U.S. universities, hospitals, cancer centers, specialized networks and research consortia, and other sites, as well as research in more than 20 other countries. NCI's two intramural divisions—the Center for Cancer Research[282] and the Division of Cancer Epidemiology and Genetics[283]—conduct basic, translational, clinical, and population research aimed at fundamental discoveries related to cancer causes and mechanisms, genetics, and host immunological and other responses to cancer. Both divisions seek to translate those findings rapidly into new preventive and detection methods and therapies. In addition, NCI provides infrastructure to help the cancer research community, both in the U.S. and abroad, take advantage of the potential benefits of emerging technologies (e.g., genomics, proteomics, bioinformatics, molecular imaging).

Cancer research conducted or supported by other NIH ICs is wide-ranging and often coordinated with NCI programs and grantees. Examples of cancer research within other ICs include:

- FIC: global research and research training related to tobacco control and research training related to chronic, noncommunicable diseases, including cancer
- NHGRI: epidemiological and genomic research on cancers
- NHLBI: research on blood-related cancers, on bone marrow transplantation as treatment for cancers, and on chronic obstructive pulmonary disease (COPD) and lung cancer; administrative coordinator of the NIH Women's Health Initiative,[284] which examined outcomes for breast and colorectal cancers
- NIA: research on the biology of aging as it relates to cancer—for example, progeroid syndromes and other conditions that increase cancer susceptibility
- NIAAA: research on the role of alcohol in colorectal, breast, esophageal, liver, and pancreatic cancers
- NIAID: research on cancer-related viral pathogenesis as well as basic biomedical research
- NIAMS: research on skin and bone cancers
- NIBIB: imaging, bioinformatics, and drug delivery technology development in areas that are vital to cancer research
- NICHD: research on reproductive organ cancers, preservation of fertility in cancer patients, and pediatric cancers
- NIDA: research on the prevention and treatment of tobacco addiction as a means of cancer prevention
- NIDCD: research on the impact of head and neck cancers on deafness and communication disorders
- NIDCR: research on oral, oropharyngeal, and salivary cancers
- NIDDK: research on diseases of the liver, prostate, kidney, colon, and bladder and their links to cancer, as well as research on diabetes, obesity, and other conditions that may increase cancer risk
- NIEHS: research on the effects of biological, chemical, or physical agents that can lead to cancer, including preparation of the National Toxicology Program's (NTP's) legislatively mandated *Report on Carcinogens*, which lists chemicals as known or reasonably anticipated to be human carcinogens
- NIGMS: cancer-related basic biomedical research
- NIMH: research on mood disorders in relation to cancer and cancer treatment

[282] http://ccr.cancer.gov/.
[283] http://dceg.cancer.gov/.
[284] http://www.nhlbi.nih.gov/whi/.

- NIMHD: research on cancer in diverse populations and on health disparities in cancer incidence, prevalence, morbidity, and mortality
- NINDS: research on brain, spinal cord, and pituitary cancers
- NINR: research focused on understanding the underlying biological mechanisms of a range of symptoms, their effect on patients, and the biological and behavioral bases for how patients respond to symptoms in cancer and cancer treatments
- NLM: research on computerized analysis and classification of cervical tissue and development of advanced imaging tools for visualization of complex 3-D volume data

NIH Funding for Cancer Research

NIH funding for cancer research was $5,621 million in FY 2012 and $5,274 million in FY 2013.[285]

Summary of NIH Activities

Across NIH, cancer and cancer-related research activities are focused on two overarching goals: (1) prevent cancer at every opportunity and (2) ensure the best outcomes for those diagnosed with cancer. Specific objectives related to these goals include understanding the causes and mechanisms of cancer, accelerating progress in cancer prevention, improving early detection and diagnosis, developing effective and efficient treatments, and building infrastructure for cancer research.

Cancer results from the complex interplay of genetic background and environmental factors. In some cases, a mutation of a single gene may be enough to increase cancer risk, whereas in other cases, combinations of gene variants collectively contribute to an individual's susceptibility to disease. A myriad of factors can influence cancer risk. In addition to carcinogens, such as those found in tobacco, and some infectious agents, physiological changes related to obesity or other factors also can play a role in initiating molecular aberrations in a cell's genome.

[285] http://report.nih.gov/categorical_spending.aspx.

Research that improves our understanding of these causes and mechanisms of cancer—from identifying novel risk factors to elucidating the processes of metastasis (the spread of cancer from the primary tumor site)—is essential for the development and application of interventions to prevent cancer's initiation and progression. NIH's plan for deciphering the causes and mechanisms of cancer includes fundamental research into cell signaling that can provide important insights into the molecular regulators of cell growth and differentiation in a range of tissues. In addition, NIH supports studies in molecular epidemiology to define complex risk factors, research on the tumor macroenvironment and microenvironment, research to understand the role of altered gene expression in cancer progression, and studies exploring the roles of susceptibility genes in cancer risk and initiation.

In an effort to bring attention to understudied and perplexing scientific questions across the continuum of cancer research, NCI launched the Provocative Questions (PQ) initiative in 2011.[286] The PQs were identified through workshops with the extramural cancer research community and were intended to represent important, but nonobvious, questions that would stimulate NCI's research communities to use laboratory, clinical, and population sciences in especially effective and imaginative ways. Two subsequent PQ Request for Application issuances were published in 2012 and 2013. While it is still too early to determine the long-term impact of the PQ initiative, increased research and attention on PQ topic areas already has shown signs of contributing to new discoveries, technologies, and progress against cancer. In addition, posing specific questions to the cancer research community has proven to be an effective and well-received method for NCI to solicit applications on targeted subjects.

[286] http://provocativequestions.nci.nih.gov/.

Recalcitrant Cancer Research

In response to the mandate under Sec. 417G (d)(1) of the PHS Act to provide information on actions undertaken to carry out 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 grants funded in FYs 2012 and 2013
- Assessment of progress in these research fields
- An update on activities in these research fields

Identifying the Molecular Basis of Cancer

One of the largest challenges facing cancer research today is dissecting the molecular changes that turn normal, healthy cells into cancer cells. The Cancer Genome Atlas (TCGA),[287] launched in 2006 as a collaboration between NCI's Center for Cancer Genomics and NHGRI, is the largest, most comprehensive analysis of the molecular basis of cancer ever undertaken. The aim of TCGA is to identify and catalog all of the relevant genetic alterations in many types of cancer. The genomic information generated by TCGA could fuel rapid advances in cancer research and has already led to new therapeutic targets. It has suggested new ways to categorize tumors, which might allow clinical trials to focus on those patients who are most likely to respond to specific treatments. In addition, TCGA also could yield information critical to reducing health disparities associated with cancer. In conjunction with the NCI Center to Reduce Cancer Health Disparities,[288] TCGA is working to ensure that adequate numbers of biospecimens are obtained from underserved and underrepresented populations to be included in TCGA analyses.

Additionally, publicly available TCGA data are being analyzed by multiple research groups nationwide and include promising efforts to link medical imaging characteristics to genomic data to permit noninvasive characterization linked to the cancer genome. For the latter effort, the associated medical images (CT, MRI, PET) from TCGA patients are being collected in a publicly accessible archive, The Cancer Imaging Archive. Researchers from across the country have formed specialized groups around each cancer type to develop ways of correlating the phenotypic features seen in a medical image to the genomic characteristics of the tumor. In this way, the heterogeneity of an entire tumor might be able to be evaluated and monitored as it changes over time and with treatment. The methods being explored are refinements of visually apparent features (e.g., edema, shape, necrosis) as well as automated computer extraction of hundreds of quantitative measures. Modeling these measures along with more traditional prognostic variables of outcome such as age, stage, or hormone receptor status can permit the development of more accurate clinical decision tools.

A prime example of TCGA's potential is illustrated by research targeting glioblastoma multiforme (GBM), an aggressive form of brain cancer. In the past year, GBM investigators discovered that about 10 percent of patients with one of the four subtypes of GBM are younger at diagnosis and live longer than patients with other subtypes of the disease, but their tumors are unresponsive to current intensive therapies. The molecular profile of this subtype offers new targets for developing drugs to treat this form of the disease more effectively. Research focused on breast cancer offers another illustrative example of the promise of fundamental insight offered by TCGA. Analysis conducted through TCGA of nearly 1,000 breast cancers revealed several tumor subtypes and identified molecular pathways potentially important in tumor maintenance. Interestingly, one of the more lethal subtypes identified more strongly resembled serous ovarian carcinomas than did other breast cancer subtypes, underscoring the fact that treatment decisions for these tumors should be based more on their molecular makeup than on the organ of origin. The information gleaned from these findings, as well as other rich sources of genomic data, will inform a new generation of drug discovery and treatment options for addressing ovarian cancer and some 20 other cancer types currently under study at TCGA. During 2012–2013, the TCGA network matured, with seminal manuscripts produced for a variety of tumor types by using newly available, state-of-the-art technologies to investigate most facets of the status, production, and regulation of DNA and RNA, key players in the functioning of the cell.

Many other noteworthy NIH research initiatives are underway to illuminate the mechanisms of cancer. The

[287] http://cancergenome.nih.gov/.
[288] http://crchd.cancer.gov/.

Therapeutically Applicable Research to Generate Effective Treatments (TARGET)[289] initiative seeks to identify and validate therapeutic targets for childhood cancers, such as acute lymphoblastic leukemia, acute myeloid leukemia, neuroblastoma, osteosarcoma, and Wilms' tumor. TARGET investigators have identified mutations in a class of protein kinase genes called the Janus kinases that predict relapse in high-risk children with acute lymphoblastic leukemia. A protein kinase is an enzyme that modifies and functionally changes other proteins. TARGET uses high-throughput screening technology to identify the genetic abnormalities in these pediatric cancers, as does another initiative, the Cancer Genome Characterization Initiative.[290] In addition, investigators in the Clinical Proteomic Tumor Analysis Consortium (CPTAC)[291] are analyzing the sequences and quantities of proteins in samples collected through TCGA with the goal of comprehensive proteogenomic integration. Proteogenomics is biological research that combines proteomics (study of proteins) and genomics (study of genomes). CPTAC investigators have discovered new molecular features of colorectal cancer associated with highly aggressive tumors and poor clinical outcome. In addition, CPTAC has released the largest public repository of cancer proteomic datasets on colorectal, breast, and ovarian tumors and has launched the first community Web-based portal of standardized multiplex proteomic targeted assays that serves as a global resource of methodologies and performance data to cancer-associated targets.

The Cancer Target Discovery and Development Network[292] is accelerating the transition of molecular data to new treatments through gene validation studies as well as from high-throughput screening of small molecules and research using mouse models. A number of other NCI resources also support studies in mouse models. The Mouse Models of Human Cancers Consortium[293] promotes the use of genetically engineered mice for mechanistic studies, as well as to provide insight into new therapeutic strategies before they are tested in clinical trials. Collaborative Cross and Diversity Outbred mice developed with NCI funding are being used to ascertain genetic determinants of therapeutic response and adverse events. Collaborative Cross mice that were developed in partnership with NIEHS and NIDA are also being used for mouse GWAS to expose the gene, gene-gene, and gene-environment contributions to cancer susceptibility that are linked to lifestyle factors, such as obesity, stress, diet, and lack of exercise.

While NCI is still conducting GWAS to identify genetic variants associated with cancer risk, sequencing efforts also have increased. To leverage these resources and ensure that the dramatic advances in genomics are incorporated into rigorous population-based studies, data from these initiatives are being made available to both intramural and extramural research scientists, as well as to investigators in the private sector, through rapid posting to databases. Ultimately, findings from these studies may yield new preventive, diagnostic, and therapeutic interventions for cancer.

Systems biology is a rapidly evolving discipline seeking a more holistic understanding of the complexities and interactions of cancer. Together with newly developed mathematical models, systems biology promises new fields of study that will increase our understanding of the causes and mechanisms of cancer. These disciplines focus on biological and genetic networks that can be measured,

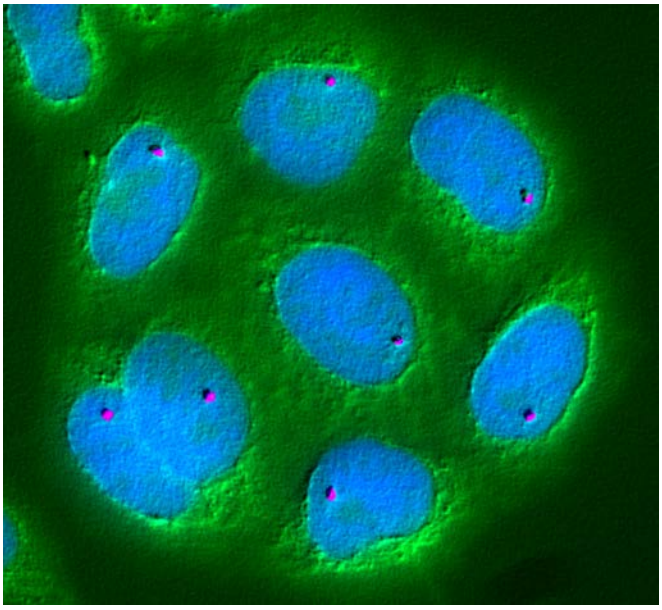


Figure 3-1. *Mapping the position of genes in the cell nucleus sheds light on basic principles governing the genome. Here, a single gene called Pem (purple) has been localized using fluorescence in situ hybridization. DNA is stained blue; the cell cytoplasm is stained green. Credit: NCI.*

[289] https://ocg.cancer.gov/programs/target.
[290] http://cgap.nci.nih.gov/cgci.html.
[291] http://proteomics.cancer.gov/.
[292] https://ocg.cancer.gov/programs/ctd2.
[293] http://www.nih.gov/science/models/mouse/resources/hcc.html.

modeled, and manipulated, rather than focusing on the individual components. Because this research requires multidisciplinary teams of experts in biology, medicine, engineering, mathematics, and computer science, NIH launched the Integrative Cancer Biology Program (ICBP)[294] to develop a framework for these activities. ICBP has funded 12 integrative biology centers around the U.S. to provide the nucleus for the design and validation of computational and mathematical models of cancer. The cellular and molecular interactions can be found and their associations with cancer tested and quantified, and parallel association studies can be conducted in relevant human populations.

In 2012, NIH established the Living Lab for Structural Biology in partnership with FEI, an Oregon-based instrumentation company, to use advanced imaging technology. It allows researchers to tackle previously unanswered questions in structural biology by creating 3-D shapes of various molecular machines. Visualizing tiny details is a step toward understanding the molecular origins of disease.

NIH is expanding its research portfolio related to the basic biology of tumor stem cells (also referred to as tumor-initiating cells). Tumor stem cells may cause recurring malignancy in some cancers. These cells often are resistant to standard chemotherapeutic agents, but may contain unique target molecules that allow their eradication with novel molecular therapeutics. Progress has been made in identifying tumor stem cells in multiple myeloma, acute myeloid leukemia, and breast cancer. NCI is expanding its research portfolio of oncolytic viruses to eradicate tumor stem cells. Oncolytic measles viruses, engineered to recognize cell surface markers on tumor stem cells, have successfully targeted and eradicated tumor stem cells in hepatocellular carcinoma.

Basic research is unlocking our understanding of what happens in the cellular microenvironment in and around a developing tumor. One aspect of this research is finding ways to boost the body's own immune responses to cancer that offer a new array of cancer treatments. The molecule CTLA-4, for example, inhibits the actions of T cells, part of the body's self-defense against tumors. Research on antibodies that block CTLA-4's action and allow the body to ramp up its own T-cell attacks on tumors led to the recent approval of the drug ipilimumab for melanoma. Clinical trials using ipilimumab and other anti–CTLA-4 antibodies are also underway for some lung and prostate cancers. Interestingly, cancer cells and activated immune cells share similar metabolic requirements. An emerging area of cancer immunotherapy is investigating whether metabolic reprogramming of immune cells can avoid competition between immune cells and cancer cells in the tumor microenvironment and lead to more effective cancer immunotherapies. Adoptive T-cell therapies are a rapidly developing form of cancer treatment in which a cancer patient's own T cells are collected, expanded, and activated in vitro and then infused into the patient to enhance the immune elimination of cancer cells. In one form of adoptive T-cell therapy, patients' T cells are genetically engineered to express potent antigen receptors, known as chimeric antigen receptors, or CARs, that target specific antigens on cancer cells. These therapeutic strategies allow the customization of the treatment approach for each patient and leverage NCI's expertise in cancer biology, immunology, synthetic biology, and antigen receptor design and in clinical medicine.

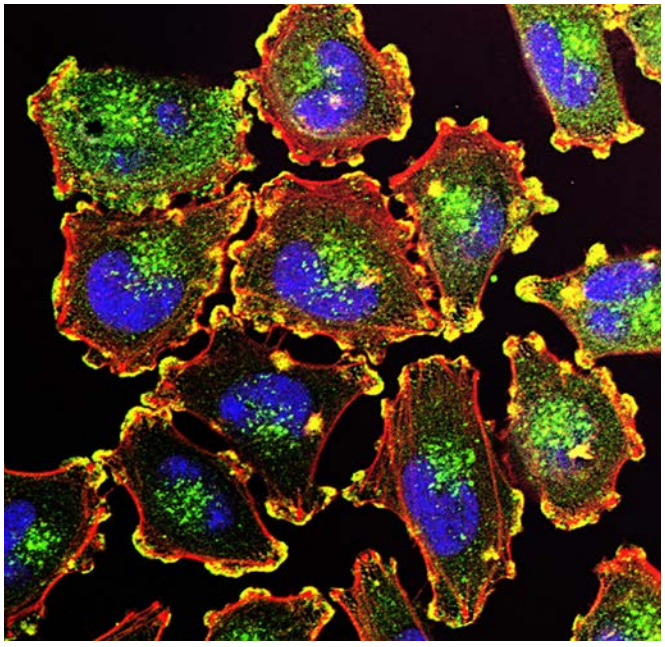


Figure 3-2. *The ability of cancer cells to move and spread depends on actin-rich core structures, such as the podosomes (yellow) shown here in melanoma cells. Cell nuclei (blue), actin (red), and an actin regulator (green) also are shown. Credit: NCI.*

[294] http://icbp.nci.nih.gov/.

Molecular profiling is an ongoing effort at NIH, from work at the bench to larger initiatives. In the area of molecular diagnostics, the NCI Early Detection Research Network[295] brings a collaborative approach to the discovery, development, and validation of early-detection biomarkers for clinical application. The Network is developing new ways of detecting cancer during its earliest stages, building a resource of cancer biospecimen reference sets for clinical studies, and driving the application of biomarkers into clinical decision-making in medical practice. Another NIH program, Strategic Partnering to Evaluate Cancer Signatures,[296] focuses on confirming, evaluating, and refining "signatures" derived from the molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes. In addition, the Cancer Genome Anatomy Project[297] focuses on determining the gene expression profiles of normal, precancerous, and cancerous cells to improve detection, diagnosis, and treatment. The Cancer Genome Anatomy Project website makes tools for genomic analysis available to researchers worldwide.

NIH CC specializes in studying and treating rare diseases—cancers among them—because of its unique capabilities to accommodate and treat a large number of cancer patients that might otherwise be seen only sporadically in more regional facilities. In 2013, the NCI Rare Tumors Initiative was started to foster closer collaborations among basic and clinical scientists and patient advocacy groups in the field of rare diseases to provide better characterization of rare tumors and facilitate the development of therapeutic approaches. Knowledge gained from this initiative can also be applied to common cancers that have similar molecular alterations. The overarching strategy is to combine and leverage the talents of intramural investigators with expertise in genetics, genomics, molecular biology, imaging, tumor models, pharmacokinetics, pharmacodynamics, biomarkers, and clinical trial development and execution. Upon successful completion of the initial pilot phase on RAS-related tumors, the scope of the Rare Tumors Initiative will broaden to include the study of additional rare tumors and will expand collaborations with intramural and extramural researchers and patient advocacy groups, with the goal to successfully study rare diseases and develop effective therapies.

[295] http://edrn.nci.nih.gov/.
[296] http://cdp.cancer.gov/scientific_programs/specs/default.htm.
[297] http://cgap.nci.nih.gov/.

Understanding and Managing Cancer Risks

While it is important to understand the molecular basis of cancer, these molecular transitions are only part of the picture. To better prevent and treat cancer, scientists need to understand the complex combination of factors in genes, environment, and behavior that puts a person at risk for developing cancer. For reasons that are self-evident, the optimal strategy for individuals, caregivers, and society at large is to prevent cancer. To this end, NIH research has multiple aims, including identifying and modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting the cancer process through early medical intervention.

One major NIH initiative anchored to the goal of clarifying environmental and genetic risk factors for cancer is the NIEHS-led Sister Study,[298] which focuses on breast cancer. This study involves a cohort of 50,000 sisters of women who have been diagnosed with breast cancer. Researchers are following these unaffected sisters over time with periodic health updates. The researchers will compare the women who develop breast cancer during the follow-up period with the women who remain healthy to identify factors associated with increased cancer risk. One finding of the study is that looking for a certain blood biomarker for DNA methylation holds promise for breast cancer detection and risk prediction.[299]

NIH also supports a network of Breast Cancer and the Environment Research Program (BCERPs)[300] to study the effects of environmental exposures from the prenatal period through adulthood that may predispose a woman to breast cancer.

Initially established in 2003 through a collaboration involving NCI and NIEHS, BCERP centers undertake multidisciplinary studies of the genetic, chemical, physical, and social factors that affect breast development during puberty and breast cancer predisposition. An important goal is to develop public health messages to educate young girls and women who are at high risk of breast cancer about the role of specific environmental stressors in breast cancer and how to reduce exposure to those stressors.

[298] http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm.
[299] Xu Z, et al., *J Natl Cancer Inst*. 2013;105(10):694–700. PMID: 23578854.
[300] http://www.niehs.nih.gov/research/supported/centers/breast-cancer/index.cfm.

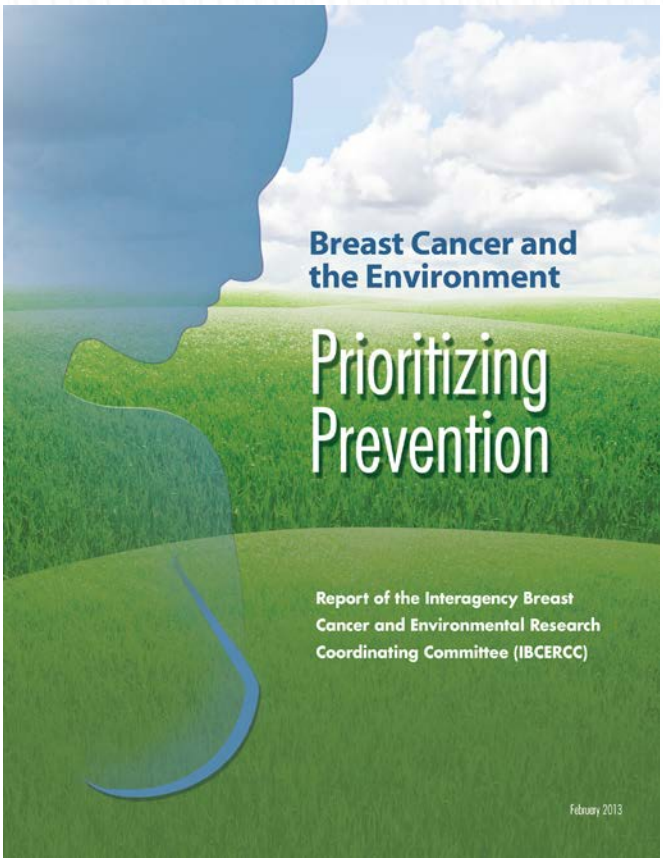


Figure 3-3. *An NIH report, Breast Cancer and the Environment: Prioritizing Prevention, recommends research, policy, and communication to help women better understand their risk of breast cancer. Credit: NIEHS.*

The Interagency Breast Cancer and Environmental Research Coordinating Committee was established by Congress in 2008 and is co-led by NCI and NIEHS. The Committee was charged with reviewing the state of the science and investments by federal agencies and other organizations and making recommendations to the Secretary of HHS for actions to better understand how changing environmental circumstances affect breast cancer risk. The Committee's report, *Breast Cancer and the Environment: Prioritizing Prevention*, details themes for future investigation in transdisciplinary research, funding for breast cancer research, and approaches for disseminating research progress to inform policy and the public so that people can make evidence-based decisions about the environment and breast cancer.[301]

[301] http://www.niehs.nih.gov/about/assets/docs/breast_cancer_and_the_environment_prioritizing_prevention_508.pdf.

Salivary gland cancers are a group of rare malignancies with few therapeutic options. The rarity of this cancer, and thus of sample availability, has been a major challenge in advancing research on salivary gland tumors. NIDCR has established a centralized Salivary Gland Tumor Biorepository at M.D. Anderson Cancer Center that collects biospecimens from several medical institutions and supports a researcher-physician-patient alliance known as the Salivary Gland Carcinomas Consortium.[302] NIDCR-supported scientists in the consortium recently published the mutational landscape of one type of salivary gland cancer called adenoid cystic carcinoma.[303, 304]

NCI also supports research to explore the effects of obesity and energy balance on cancer risk, as well as to inform the development of improved methods for assessing energy intake, fat distribution, physical activity, and sedentary behavior. For example, NCI is conducting etiologic studies in large prospective cohorts and through multicohort consortia, performing mechanistic studies using known biomarkers, and searching for novel biomarkers. These concerted efforts, along with other analytic approaches, explore the exposures in prospective studies of certain cancers (e.g., pancreatic cancer, esophageal cancer) and are refining our understanding of the relationships of these cancers with other more common cancers (e.g., post-menopausal breast cancer, colon cancer). An example of a program in this area is the Transdisciplinary Research on Energetics and Cancer[305] initiative, which was developed to foster collaboration among scientists and accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet.

One role of the trans-HHS National Toxicology Program (NTP), led by NIEHS, is to review the cumulative state of the science on the potential carcinogenicity of substances that people may be exposed to in their daily lives, such as industrial and commercial chemicals, biologics, dietary supplements, and environmental contaminants. Determinations are made as to whether a substance is a known human carcinogen or a reasonably anticipated

[302] https://research.mdacc.tmc.edu/Salivary_DB/.
[303] Stephens PJ, et al. *J Clin Invest*. 2013;123(7):2965–8. PMID: 23778141.
[304] Ho A, et al. *Nat Genet*. 2013;45(7):791–8. PMID: 23685749.
[305] http://www.trecscience.org/trec/default.aspx.

human carcinogen, and these findings are published in the publically available *Report on Carcinogens*.[306] NTP conducts and publishes other research related to cancer. In FY 2013, NTP released the results of a literature-based evaluation on the developmental effects and pregnancy outcomes associated with the use of cancer chemotherapy during pregnancy.[307] The program also released a study that developed a model for arsenic-induced kidney cancer[308] and another study that showed cancerous epithelial cells can cause normal stem cells to develop cancer-like characteristics by being in close proximity.[309] These studies are important for understanding the potential mechanisms of cancer.

NCI has been a long-standing supporter of the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans. The IARC Monographs program critically evaluates the published scientific evidence on carcinogenic hazards to humans, including chemicals, complex mixtures, physical agents, biological organisms, behaviors and lifestyle factors, and environmental exposures and occupations. The Monograph volumes are considered critical references that inform health policy and cancer research worldwide about carcinogenic risks to reduce cancer burden globally. In FY 2013, IARC assessed and classified specific herbal products as possibly carcinogenic to humans based on a number of studies conducted by NTP.[310]

Dramatic developments in technology and an enhanced, continually evolving understanding of the causes and mechanisms of cancer are proving crucial to the development of prevention strategies. Research across multiple disciplines will provide a more complete understanding of the interplay of molecular, behavioral, genetic, and other factors that contribute to cancer susceptibility. Identifying critical molecular pathways in precancerous lesions will provide new drug targets for preempting cancer. For example, the recent characterization of ovarian tumors through TCGA may inform the development of a much needed screening assay for this disease, which is currently often detected in late stages. Genomic studies also may identify targets for chemoprevention. The Consortia for Early Phase Prevention Trials,[311] first funded in 2003, was renewed in 2012 with five major cancer research centers chosen to lead new studies through multiple collaborative networks to assess the cancer prevention potential of new agents, with a focus on Phase I and Phase II clinical trials. In addition to designing and conducting trials and recruiting participants, the Consortia work to (1) characterize the effects of potential agents on molecular targets, (2) identify biological events associated with cancer development, (3) develop scientific insights into the mechanisms of cancer prevention by the agents examined, and (4) correlate these effects with clinical endpoints to bring these findings into clinical practice.

A major step forward in our efforts to prevent cancer has been the development of vaccines that target human papillomavirus (HPV). Persistent infection with HPV is recognized as the major cause of cervical cancer. Gardasil®, an FDA-approved vaccine against HPV types 6, 11, 16, and 18 (the viral types that cause approximately 70 percent of cervical cancers and 90 percent of genital warts), and Cervarix®, an FDA-approved vaccine against HPV 16 and 18, are now available. Given recent evidence that oropharyngeal cancers are increasingly associated with HPV infection, NIDCR supports research on HPV and has shown that Gardasil® and Cervarix® are effective in preventing infection by the HPV strains associated with these cancers.[312] Other similar vaccines against HPV types 16 and 18, as well as vaccines that address additional subtypes, are in development. These vaccines have the potential to save thousands of lives annually in the U.S. and several hundred thousand more lives each year worldwide. All of these vaccines resulted directly from epidemiological, basic, and preclinical research discoveries, as well as the development of a prototype HPV vaccine, by NIH scientists.

In an effort to reduce the cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet, NIH has funded the Transdisciplinary Research on Energetics and Cancer Research Centers, which foster collaboration among transdisciplinary teams of scientists. The Centers are studying factors that lead to obesity

[306] http://ntp.niehs.nih.gov/go/roc.
[307] http://ntp.niehs.nih.gov/ntp/ohat/cancer_chemo_preg/chemopregnancy_monofinal_508.pdf.
[308] Tokar EJ, et al. *Chem Res Toxicol*. 2013;26(1):96–105. PMID: 23137061.
[309] Xu Y, et al. *Environ Health Perspect*. 2013;121(8):944–50. PMID: 23687063.
[310] IARC. *Lancet Oncol*. 2013;14(9):807–8. PMID:24058961.
[311] http://prevention.cancer.gov/programs-resources/programs/phase-0-I-II.
[312] Herrero R, et al. *PLoS One*. 2013;8(7):e68329. PMID: 23873171.

and the mechanisms by which obesity increases the risk of cancer. The initiative is connecting with a number of established projects in the areas of diet, physical activity, and weight and is integrated with the *Strategic Plan for NIH Obesity Research*.[313]

The knowledge that environment and behavior can play critical roles in the development of cancer has been fundamental to one of the greatest public health success stories of the 20th century: the reduction in tobacco use and related diseases. Since the publication of the first *Surgeon General's Report on Smoking and Health* in 1964, tobacco control efforts in the United States have included restrictions on smoking in public places, increases in cigarette excise taxes, limits on underage access to cigarettes, and efforts to increase public awareness of the hazards of smoking. According to researchers from the NCI-sponsored Cancer Intervention and Surveillance Modeling Network (CISNET), 20th century tobacco control programs and policies have been responsible for preventing nearly 800,000 lung cancer deaths in the U.S. from 1975 through 2000.[314] This success has been due to public-private partnerships and also is a trans-HHS victory, as significant research investments have been made over the past 50 years by NCI, NIEHS, NHLBI, NIDA, NIAAA, CDC, and AHRQ. In addition, untold numbers of cancer-related illnesses and deaths have been prevented through the decrease in exposure of nonsmokers to environmental tobacco smoke due to recognition of the effects and widespread campaigns to limit or ban smoking in public places. Without these investments, millions of Americans might still be smoking today, hundreds of thousands of smokers and those exposed with them would have died prematurely of a tobacco-related disease, and billions of dollars would have been spent on providing treatment to people with tobacco-related illnesses.

NIH is strengthening health research infrastructure and building global research capacity through FIC's International Tobacco and Health Research and Capacity Building Program, which identifies new approaches in prevention and treatment through international collaborative research. This program promotes transdisciplinary approaches to reduce the global burden of tobacco-related illness and is designed to promote international cooperation between U.S. investigators and scientists in low- and middle-income countries (LMICs) where tobacco consumption is a current or anticipated public health problem. The program also requires and underscores the need to build research capacity to support locally relevant research on tobacco control interventions and enhance the number and the knowledge of tobacco investigators in LMICs.

Improving Screening, Diagnosis, and Treatment

Detecting and diagnosing tumors early in the disease process, before the tumor becomes invasive and metastatic, can dramatically improve a patient's odds for successful treatment and survival and prevent a large proportion of cancer deaths. Therefore, NIH seeks to accelerate the translation of basic research findings into sophisticated, minimally invasive procedures that harness imaging, genomic, proteomic, nanotechnology, and other advanced early detection and diagnostic techniques. These improvements in screening and diagnosis, together with NIH's continuing support of new and improved cancer treatments, have the potential to greatly improve outcomes for cancer patients.

In support of this goal, the Physical Sciences-Oncology Network (PS–ON) supports innovative ideas that blend perspectives and approaches from the physical sciences and cancer research, with the goal of improving cancer prevention, detection, diagnosis, prognosis, and therapy. PS-ON investigators develop and test physical sciences-based experimental and theoretical concepts that complement and advance our current understanding of cancer biology and oncology. Using advanced microscopy techniques and computational analysis of the signaling within the cell, researchers have been able to determine the best schedule for radiation treatment in glioblastoma patients. In a similar vein, the Innovative Molecular Analysis Technologies (IMAT) program[315] is a high-risk and high-reward approach to supporting new technologies that serve the broad spectrum of cancer research. Grant awards from the IMAT program support roughly 25–30 highly innovative technology research projects each year, selected for their

[313] http://www.obesityresearch.nih.gov/About/StrategicPlanforNIH_Obesity_Research_Full-Report_2011.pdf.
[314] Holford TR, et al. *JAMA*. 2014;311(2):164–71. PMID: 24399555.
[315] http://innovation.cancer.gov/.

strong potential to transform cancer research and/or clinical care of cancer patients. Since the program's inception, NCI has awarded more than 500 IMAT grants, leading to more than 100 platforms that are now either commercially available or accessible through collaboration with NCI-supported scientists.

Another program, the Cancer and Imaging Program,[316] supports cancer-related basic, translational, and clinical research in imaging sciences. Program initiatives include (1) development and delivery of image-dependent interventions for malignant and premalignant conditions; (2) standardized models for the design of clinical trials that use imaging technologies; (3) development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and (4) development of imaging methods for cancer detection and treatment and for monitoring responses to therapy.

In June 2013, the NCI Board of Scientific Advisors (BSA) approved the creation of the NCI Community Oncology Research Program (NCORP). The overall goal of NCORP is to bring state-of-the art cancer prevention, control, treatment and imaging clinical trials, cancer care delivery research, and disparities studies to individuals in their own communities. This new program expands upon the success of the Community Clinical Oncology Program (CCOP) Network[317] (including its minority-based [MB] CCOPs), adding elements of the NCI Community Cancer Centers Program (NCCCP)[318] and creating a network for cancer care delivery research. NCORP replaces both the CCOP Network and NCCCP. Similar to the CCOP and MB-CCOP networks, NCORP's three major components include research bases, community sites, and minority/underserved community sites, with the community sites having the capacity to support cancer care delivery research. The proposed timeline for implementing this new program included releasing the FOA in fall 2013 and conducting the review and awards in summer 2014.

The Cancer Research Network (CRN)[319] conducts cancer prevention, early detection, treatment, long-term care, and surveillance research using data systems of nine HMOs nationwide. Studies of lifestyle change include research into energy balance (integrated effects of diet, physical activity, and genetics on growth and body weight) as a way to control cancer incidence. The SEER Program,[320] which has collected data since 1973, regularly samples approximately 28 percent of the U.S. population, including 26 percent of African Americans, 38 percent of Hispanics, 44 percent of American Indians and Alaska Natives, 50 percent of Asians, and 67 percent of Hawaiian/Pacific Islanders. This database provides critical data on cancer trends and is maintained by NCI in collaboration with CDC's National Center for Health Statistics, the Census Bureau, and the North American Association of Central Cancer Registries.

Screening for cancers within the large population of people who do not have obvious cancer symptoms represents a major undertaking for health care providers in the U.S. Most medical organizations, including the U.S. Preventive Services Task Force (USPSTF), recommend screening for breast, colon, lung, and cervical cancers based on demonstrated mortality reductions in randomized trials (breast, colon, and lung cancers) and large population cohort studies (cervical cancer). Evidence shows that the process of finding these cancers among the many people screened is not optimal. In the areas of cancer screening and malignancy management, research is critically needed to establish minimally invasive methods to predict whether a screen-detected lesion is indolent, requiring only careful monitoring, or is aggressive/progressive, thus requiring appropriate intervention. To address what is called *overdiagnosis*—detecting lesions that will not cause symptoms or threaten life and therefore do not need treatment—NCI is developing a research initiative to establish a comprehensive approach to the molecular and cellular characterization of screen-detected lesions, with the goals of enabling better prediction of the fate of early lesions as well as maximizing the benefits of screening while minimizing the harms.

Although the performance characteristics of individual screening tests (sensitivity, specificity, and positive predictive value) are relatively well known, analogous performance characteristics of the entire screening process remain understudied. To pursue the long-term objective of

[316] http://imaging.cancer.gov/.
[317] http://ccop.cancer.gov/.
[318] http://ncccp.cancer.gov/.
[319] http://crn.cancer.gov/about/.
[320] http://seer.cancer.gov/.

optimizing the screening processes in community practice, NIH is supporting Population-based Research Optimizing Screening through Personalized Regimens Research Centers.[321] This multisite, coordinated, transdisciplinary initiative has the scientific goal of supporting research to better understand how to improve the screening process (i.e., recruitment, screening, diagnosis, referral for treatment) for breast, colon, lung, and cervical cancers.

Surprisingly, some research into the causes and mechanisms of cancer has revealed that tumors function like organs, comprising many interdependent cell types that contribute to tumor development and progression. The relationship between tumors and their surrounding cellular environment evolves over time, strongly influencing tumor progression, metastatic potential, and responsiveness to treatment. The Tumor Microenvironment Network[322] is an NIH program focused on expanding our understanding of the role of the microenvironment in which a tumor originates and the critical role the microenvironment plays during tumor development, progression, and metastasis and in conferring therapeutic resistance.

Furthermore, interest is growing in the scientific community about the relationship between inflammation and cancer. Inflammation is a response to tissue damage, whether resulting from physical injury, infection, exposure to toxins, or other types of trauma. NIH is pursuing research on the links between carcinogenesis and alterations in the microenvironment induced by inflammation. Current research on inflammation suggests that pro-inflammatory conditions contribute to the development of several types of cancer, including lung, stomach, and liver cancers, and may lead to new treatment approaches (for example, research efforts focused on inflammatory and fibrotic diseases of the esophagus, stomach, colon, pancreas, and liver—all of which are risk factors for the development of cancer in these organs). The Cancer and Inflammation Program[323] constitutes a major component of NIH's inflammation and cancer initiative, which partners expertise in inflammation and immunology with cutting-edge cancer etiology and carcinogenesis research.

NCI has a growing basic research portfolio on both AIDS-defining and non–AIDS-defining cancers. With increased survival as the result of widespread use in the developed world of highly active antiretroviral therapy (HAART), non–AIDS-defining cancers (i.e., anal cancer, liver cancer, lung cancer, skin cancer, Hodgkin's disease) are on the increase in the HIV-infected population. NCI's growing focus on liver cancer as the result of infection by hepatitis B virus (HBV) or hepatitis C virus (HCV) is illustrated in the HHS plan *Combating the Silent Epidemic of Viral Hepatitis: Action Plan for the Prevention, Care, & Treatment of Viral Hepatitis*.[324] Accomplishments thus far include workshops on viral hepatitis and liver cancer as well as FOAs encouraging new areas of research within the NCI portfolio.

NCI is also investigating therapies that use host immune cells and responses to combat tumor growth and metastasis. For example, the Center of Excellence in Immunology[325] within the IRP, fosters the discovery, development, and delivery of novel immunologic approaches for the prevention and treatment of cancer and cancer-associated viral diseases. The complex interactions between tumors and surrounding cells that influence cancer progression are being characterized by projects funded through ICBP and the Tumor Microenvironment Network. Projects funded through the recent Advanced In vivo Imaging to Understand Cancer Systems initiative are focused on integrating advanced in vivo imaging technologies with systems biology approaches to understand complex cancer phenomena at the highest resolution. Advocacy by the Center of Excellence in Immunology, in partnership with NCI and NIAID, resulted in methods for producing the immune signaling molecule IL-15 in a manner that is safe for human use. Through the Cancer Immunotherapy Trials Network, clinical-grade IL-15 is now used for both intramural and extramural clinical trials to boost the immune system's innate cancer-fighting capabilities.

Another area of research that holds promise for advancing molecular diagnostics is proteomics—the study of complex arrays of proteins produced by cells and tissues. Since its completion nearly a decade ago, the Human Genome Project has catalyzed progress in proteomics research, and

[321] http://appliedresearch.cancer.gov/networks/prospr/.
[322] http://tmen.nci.nih.gov/.
[323] http://ccr.cancer.gov/labs/lab.asp?labid=790
[324] http://www.hhs.gov/ash/initiatives/hepatitis/index.html.
[325] https://ccrod.cancer.gov/confluence/display/COEI/Home.

NIH has taken a leading role in facilitating the translation of proteomics from laboratory research to clinical application through the Clinical Proteomic Technologies for Cancer initiative. The overall objective of this initiative is to build a foundation of standardized proteomic technologies and workflows, develop advanced proteomic technologies and computational tools, and develop broadly available resources (well-characterized affinity reagents, instrument reference materials, and data reference sets) for the cancer research community. These activities, which are needed to advance our understanding of protein biology in cancer and accelerate the development of clinical applications, are conducted through a collaborative approach of a multidisciplinary network of teams and individual investigators. Deliverables include reference materials, open-source computational tools, proteomics data-sharing principles, improved quality control of biospecimens for proteomic experiments, regulatory science documents, and publicly available antibodies.[326]

As previously noted, efforts at NIH—particularly at NCI and NIDA—to study and reduce the use of tobacco products have contributed to a sustained annual reduction in age-adjusted cancer mortality rates over the past decade and more—not just among men, in whom we have seen steady declines, but now also among women. Unfortunately, women have a more difficult time quitting smoking than men do. One contributing factor is that nicotine replacement therapies are more effective for men than for women. Thus NIDA researchers are investigating alternative treatments, both pharmacologic and behavioral, as well as barriers to smoking cessation for women. For example, three researchers funded through the Office of Research on Women's Health (ORWH) Specialized Centers of Research on Sex Differences[327] are investigating new smoking cessation medications that are showing promise as effective smoking cessation treatments in women.

Current and former heavy smokers still remain at high risk of developing lethal lung cancers, which are the leading cause of cancer mortality. The recently completed National Lung Screening Trial (NLST)[328] provided the first clear demonstration that a screening procedure among this high-risk population can be effective in reducing mortality from lung cancer. Current and former heavy smokers who were screened with low-dose helical computed tomography (CT) were 20 percent less likely to die of lung cancer than were peers who received standard chest X-rays. This promising finding, combined with proven tobacco prevention and cessation efforts, could save many lives among those at greatest risk. USPSTF commissioned modeling studies of lung cancer screening by investigators in NCI's CISNET to fully assess the risks and benefits of screening with low-dose helical CT and provide information about the optimum age at which to begin and end screening, the optimum screening interval, and the relative benefits and harms of different screening strategies. In 2013, USPSTF considered the NLST results and the CISNET modeling studies, along with a systematic review of the literature. USPSTF concluded that annual screening for lung cancer with low-dose CT is of moderate net benefit in asymptomatic persons who are at high risk for lung cancer based on age, total cumulative exposure to tobacco smoke, and years since quitting smoking.[329] In the coming years, NCI seeks to support a wide range of prevention and detection efforts that could have equally significant outcomes, including enhanced screening for breast, cervical, and colorectal cancers; new imaging approaches for more accurate and earlier detection of breast cancer, GBM, and renal cell carcinoma; and identification of biomarkers as early warning signs of the presence of or likelihood of developing many kinds of cancers. NCI research will continue to develop an enhanced understanding and ability to modify behaviors that increase the risk of developing cancer, reduce exposure to environmental carcinogens, and mitigate the effects of environmental or genetic cancer risks.

Developing more effective, more efficient, and less toxic cancer treatments is at the heart of NIH's cancer research agenda. A better understanding of the fundamental mechanisms leading to cancer development, progression, and metastasis is improving the identification of key biochemical pathways in the disease process as targets for treatment. Acceleration of target validation and the development of new treatment modalities are being made possible by recent advances in biomedical science and

[326] http://antibodies.cancer.gov/.
[327] http://orwh.od.nih.gov/sexinscience/researchtrainingresources/scor.asp.
[328] http://www.cancer.gov/clinicaltrials/noteworthy-trials/nlst.
[329] http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanfinalrs.htm.

technology. A rapid translation from development to delivery will ensure that promising treatments move safely and efficiently from preclinical investigation through late-stage clinical trials and into clinical practice.

NIDCR supports research to improve prevention, diagnosis, and treatment for a number of different cancers, including oral, oropharyngeal, salivary gland, and head and neck cancers. For example, use of state-of-the-art high-throughput sequencing technologies has resulted in the identification of abnormal pathways in oral cancer cells that can be targeted for cancer therapy.[330] In addition, NIDCR researchers have taken advantage of scientific advances to repurpose existing drugs, such as rapamycin and metformin, to combat these forms of cancer. NIDCR and NCI scientists are now teaming up to explore whether metformin might represent a safe, low cost, and effective treatment option to prevent the development of head and neck cancers in patients with premalignant lesions.

NIH is working on multiple fronts in the drive to develop new, more effective therapies for cancer. One innovative initiative, the NCI Experimental Therapeutics (NExT) Program,[331] combines the extensive expertise of cancer treatment and diagnosis in anticancer drug development with the dynamic NIH intramural research resources. Drug discovery and development projects that enter the NExT pipeline are focused on unmet needs in cancer therapeutics that are not addressed adequately by the private sector. NExT is designed to advance clinical practice and bring improved imaging methods and therapies to cancer patients. The discovery engine of this program is the Chemical Biology Consortium.[332] NCI has established this collaborative network comprising 12 of the top Specialized and Comprehensive Screening and Chemistry Centers with world-class capabilities covering high-throughput methods, bioinformatics, medicinal chemistry, and structural biology. The subsequent late-stage preclinical development leading to first-in-human studies of promising molecular or biologic molecules involves resources provided by the highly successful Developmental Therapeutic Program. Concurrent developments of agents for molecular imaging involving the Cancer Imaging Program[333] and/or the development and use of pharmacodynamic assays through the efforts of the Pharmacodynamic Assay Development and Implementation Section,[334] the National Clinical Target Validation Laboratory, and labs within the intramural Center for Cancer Research allow early assessment of potential clinical biomarkers. These coordinated and focused research and development (R&D) processes enable continued incorporation of new data and disease insights into every step of the discovery and development process, thereby increasing the potential for successful clinical evaluation of agents. The new Clinical Assay Development Program[335] was established to accelerate the movement of promising clinical laboratory assays from the research setting into clinical trials. The program provides access to tissue and laboratory resources for the analytical and clinical validation of assays to predict response to cancer treatment or disease outcome. Services are provided to efficiently develop diagnostic tests that address clinical needs, including co-development of targeted agents and predictive markers. Several investigator-proposed assays were taken into this program, and currently three assays are in development that, once analytically validated, could be used in clinical trials.

The Matrix Drug Screening for Combination Therapies in Cancer Initiative, launched in 2012, is a collaborative project between NCI intramural and NCATS aimed at identifying synergistic drug combinations for the treatment of cancer using a quantitative high-throughput screening approach. A novel automated technology developed by NCATS has enabled drug combinations to be screened using selected cell lines in a dose-related manner. Informatics methods are identifying antagonistic, additive, and synergistic effects of drugs in combination.

NCI investments in basic research lead to the identification of potential therapeutic targets, many of which are validated and pursued by commercial interests. With the NExT initiative and other similar programs, NCI seeks to complement, rather than compete with, the private sector and often takes the lead on high-risk projects or those focused on rare cancers. Drugs against targets that have been characterized in part by NCI-funded researchers are already being used to treat cancer and/or are being tested in clinical trials. For example, Phase III clinical trials recently

[330] Curtis R, et al. *Cancer Discov*. 2013;3:770–81. PMID: 23619168.
[331] http://next.cancer.gov/.
[332] http://next.cancer.gov/discoveryResources/cbc.htm.
[333] http://imaging.cancer.gov/.
[334] http://next.cancer.gov/developmentResources/pd_biomarker.htm.
[335] http://www.cancerdiagnosis.nci.nih.gov/scientific_programs/pacct/cadp.htm.

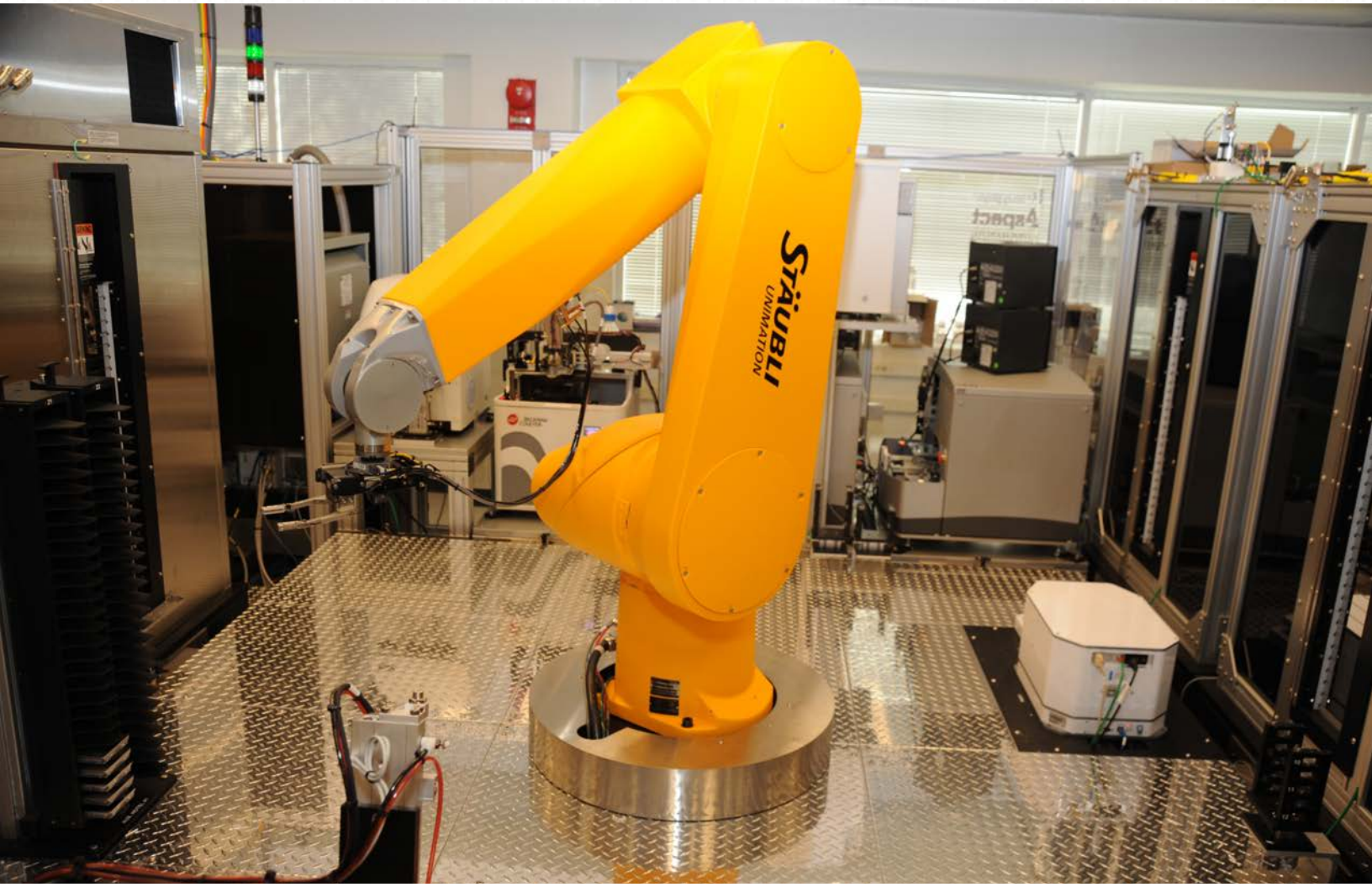


Figure 3-4. *NCATS robot for high-throughput screening of chemical compounds. Credit: NCATS.*

have been initiated to test therapies targeting the genes *BRAF* in melanoma and *ALK* in lung cancer. NCI supports a large portfolio of translational and preclinical studies that are focused on identifying, validating, and testing strategies for the treatment of cancer. The Comparative Oncology Program (COP)[336] provides an integrated mechanism through which the study of naturally occurring cancers in animals can generate new information about cancer and help translate biological concepts into clinical application. As part of this effort, and to evaluate novel therapeutic strategies for cancer, COP has established a multicenter collaborative network of extramural comparative oncology programs to design and implement preclinical trials involving domesticated animals.

The Repository of Molecular Brain Neoplasia Data (REMBRANDT)[337] is an online portal that integrates genomic data from several hundred brain tumors with clinical information about how patients responded to treatments, allowing researchers to dissect relationships between genomic traits and outcomes as well as conduct in silico investigations of potential therapeutic targets. Associated clinical images are publicly available from 130 of the cases that were used to develop an approach for correlating genomic data with phenotypic imaging data.[338] The Trial Assigning IndividuaLized Options for Treatment (Rx), or TAILORx,[339] is examining the possibility that a molecular

[336] https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Home.

[337] https://caintegrator.nci.nih.gov/rembrandt/.

[338] https://wiki.cancerimagingarchive.net/display/Public/REMBRANDT?src=contextnavchildmode.

[339] http://www.cancer.gov/clinicaltrials/noteworthy-trials/tailorx.

profiling test that examines many genes simultaneously could help predict whether women with early-stage breast cancer would benefit from chemotherapy in addition to radiation and hormonal therapy. Incorporating molecular data into clinical decision-making could spare some women unnecessary treatment if chemotherapy is not likely to impart substantial benefit.

The range of contributions that radiation oncology and radiation biology brings to cancer care and research has expanded markedly in recent years. Technological advances in imaging, treatment planning, patient immobilization/tumor tracking, and the intensity- and image-guided delivery of radiation therapy could improve routine clinical care by increasing tumor dose and reducing high doses to normal tissues. Some diseases considered to be untreatable by radiation can now be managed successfully, such as liver tumors. Proton particle therapy, with its ability to focus the radiation, is emerging across the U.S. as a potential improved means of treatment delivery for which randomized trials are underway. NCI is supporting planning grants for treatment with carbon (and other heavy) ions that have both unique physical and biological capabilities. The molecular, cellular, and systemic effects of radiation open up new means of exploiting drug-radiation studies and enhancing immunotherapy. The latter has been one of the major treatment advances within the past 2 years. The use of photodynamic therapy remains of interest, with intriguing results for treating thoracic mesothelioma being further investigated. This would represent a new paradigm in treating this disease. The Radiation Research Program[340] provides linkage and collaboration among NCI drug development programs, translational radiation oncology researchers, and industry to develop new use of drugs already in the clinic, called repurposing, and for new molecular targeted agents. Systemic radiation therapy linked to antibodies or other novel molecules, such as those from nanotechnology, offer unique approaches to targeting tumors and micro-metastatic disease.

Innovative research in genetics, imaging, and cancer molecular signatures is laying the groundwork for customized cancer patient care. The Advanced Technology Program[341] accelerates the delivery of new treatments to patients by developing and applying advanced technologies, such as biomedical imaging. The NCI imaging facility for clinical cancer research will fuse imaging and pathology in the evaluation of patients throughout treatment. The NIH Center for Interventional Oncology[342] offers new and expanded opportunities to investigate cancer therapies using imaging technology to diagnose and treat localized cancers in a targeted and minimally or noninvasive manner. This interdisciplinary environment combines training, patient treatment, and translational research and development in interventional oncology.

NCI's Alliance for Nanotechnology in Cancer, a comprehensive program involving both public and private sectors, is designed to accelerate the use of nanotechnology in cancer research and its implementation into the clinical environment. This initiative supports research on novel nanodevices to detect and determine the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective in killing those cells. Research programs of the Alliance include the Nanotechnology Characterization Laboratory, Cancer Nanotechnology Platform Partnerships, training programs, an intramural Nanotechnology Characterization Laboratory, and the Translation of Nanotechnology in Cancer Consortium.

Improving the quantitative evaluation of prediction or the measurement of response to therapy in the context of clinical trials is the mandate of the Quantitative Imaging Network (QIN). The cross-disciplinary, international, cross-institutional teams that comprise QIN, collaborate to develop and test algorithms for the quantitative evaluation or prediction of response to therapy using medical imaging. If the variability in measurements of tumor size or metabolic function in routine medical imaging methods can be reduced, fewer patients will be needed to establish the efficacy of a therapeutic intervention. QIN's goals include the correlation of quantitative imaging results with other molecular biomarker assays, including genomics. The investigators develop and validate quantitative imaging methods and correlation studies within an open science framework, positioning QIN to serve as a technical resource

[340] http://rrp.cancer.gov/.
[341] http://atp.ncifcrf.gov/.
[342] http://www.cc.nih.gov/centerio/index.html.

for clinical trials networks, such as IROC-NCTN. QIN is emerging as an effective research resource model; the awardees collect image data and metadata from current clinical trial data or retrospective trial data, develop advanced quantitative imaging methods, and reach a consensus on best practices to validate their performance. The data, tools, and methodologies are shared in the NCI Cancer Imaging Archive and the NCIP Hub. Multisite collaborations using common data sets and challenge competitions, where defined sets of images are used in a contest by different teams to apply their unique algorithms to a quantification problem, are among the methods the teams use.

A cornerstone of the infrastructure for NIH-sponsored cancer research is NCI's Cancer Centers Program, which focuses on transdisciplinary approaches to basic, population, and clinical research. Centers with comprehensive designation must have robust portfolios in each of these areas and must also demonstrate professional public education and outreach activities in the communities they serve. The 68 NCI-designated cancer centers conduct some of the highest quality basic, translational, and population research to improve cancer prevention, diagnosis, and treatment while also stimulating innovative pilot projects in new investigational areas. NCI-designated cancer centers are increasingly reaching out to community oncology practices and to minority and underserved patient populations. They are also committed to delivering high-quality care. A program has been established to pre-qualify and re-qualify annually all of the comprehensive cancer centers to perform advanced imaging so that quality of the imaging and shortened time to clinical trial initiation can be assured.

Specialized Programs of Research Excellence (SPORE)[343] grants—which are often, but not always, situated within cancer centers—are multiproject, multidisciplinary, and in some cases, multi-institutional translational research grants that focus on specific organ sites, such as breast or lung cancer; a group of highly related cancers, such as gastrointestinal (GI) cancers or sarcomas; or cancers across organ sites that are connected by common biological pathway alterations. These grants involve both basic and clinical/applied scientists (team science) within each project and support studies that will result in new approaches to prevent, detect, diagnose, and treat human cancers. There are currently 51 active SPORE grants. SPOREs within cancer centers build upon, but do not duplicate, the resources of that center.

The SPOREs foster bi-directional translational research, which means that a project may use knowledge of human biology to develop and test the feasibility of cancer-relevant interventions in humans or determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer. SPOREs create an environment for inter-SPORE collaboration and collaboration with other government and nongovernmental groups to increase cross-fertilization of ideas, leverage resources, reduce duplication, and ensure access of resources to the scientific community, ultimately facilitating the movement of SPORE research along the translational science continuum. SPOREs encourage the involvement of patient advocates and support preclinical and early-stage clinical studies focused on molecular pathways associated with organ-site specific cancers, with emphasis on therapeutic targets. New treatments are developed concomitantly with predictive markers that identify patients most likely to respond to specific treatments. Promising therapies are advanced to the NCI National Clinical Trials Network, industrial partners, or other clinical trials consortia for evaluation in later stage clinical trials. SPOREs also support novel pilot projects focused on the identification of cellular and molecular markers to improve early cancer detection, diagnosis, and risk assessment to reduce cancer incidence, morbidity, and mortality; extend survival; and increase the quality of life of cancer patients.

Clinical trials are a critical step in moving potential therapies into clinical practice. NCI supports clinical trials through a number of mechanisms that are designed to promote and support clinical trials of new cancer treatments, explore methods of cancer prevention and early detection, and study quality-of-life and rehabilitation issues. One of NCI's flagship efforts has been the Cooperative Groups, which were recently restructured and launched in early 2014 as the National Clinical Trials Network.[344] Other trials are

[343] http://trp.cancer.gov/.

[344] http://www.cancer.gov/newscenter/newsfromnci/2014/NCTNlaunch.

conducted within IRP and with extramural support of investigator-initiated projects. NCI has also implemented the Biomarker, Imaging, and Quality of Life Studies Funding Program,[345] which supports promising correlative studies related to biomarkers, imaging, patient quality of life, and cost-effectiveness analysis, in association with Phase III and large Phase II trials. In order to facilitate management and coordination of the clinical trials portfolio, NCI created the Clinical Trials Reporting Program,[346] a comprehensive database containing regularly updated information on all NCI-supported interventional clinical trials.

Improving the Quality of Cancer Care

Research on the quality of cancer care is essential to ensure the best outcomes for all people who may be affected by cancer. Research in this area includes surveillance as well as epidemiological and cost-effectiveness studies. In addition, quality-of-life research increases our understanding of the impact of cancer on patients, survivors, and their family members, many of whom are at increased risk for cancer themselves due to shared cancer-causing genes, lifestyles, or environmental exposures. Dissemination of research helps ensure that the knowledge gained through NIH-supported research is communicated appropriately and effectively to health care providers, policymakers, and the public.

CISNET[347] is a consortium of NCI-sponsored investigators that seeks to improve our understanding of the impact of cancer control interventions (e.g., prevention, screening, treatment) on population trends in incidence and mortality using statistical modeling. The network focuses on meeting the expanding scientific need for (1) tools that assist in synthesizing emerging evidence in a timely manner, due to the extraordinary pace of developments in cancer control technologies; (2) basic science studies investigating molecular and biological determinants of cancer risk; (3) upcoming results from clinical trials; and (4) new health-related data.

[345] http://biqsfp.cancer.gov/.
[346] http://www.cancer.gov/clinicaltrials/conducting/ncictrp/main.
[347] http://cisnet.cancer.gov/.

NIH focuses on cancer treatment as a primary area for quality-of-care research and the translation of research findings into practice. To this end, several collaborative projects have been initiated:

- The Quality of Cancer Care Committee, an interagency working committee that has fostered collaborative projects directly involving HRSA, AHRQ, CMS, VA, Indian Health Service, CDC, and other federal health care research and delivery agencies
- The National Quality Forum, a major public-private partnership that identifies core measures of cancer care quality
- Research on outcomes measurement by the Cancer Outcomes Measurement Working Group[348] and the Cancer Care Outcomes Research and Surveillance Consortium[349]
- Studies on improving the quality of cancer communications
- Research to monitor patterns of treatment dissemination and quality of care through Patterns of Care/Quality of Care Studies[350]

In addition, the NCI Community Cancer Centers Program[351] is researching how best to bring effective cancer treatments to patients in the communities where they live.

Due in large part to the success of new treatment strategies, the population of cancer patients surviving more than 5 years from diagnosis continues to grow. Currently, there are more than 14 million cancer survivors in the U.S., representing over 4 percent of the population. NIH supports research and education efforts aimed at professionals who care for cancer patients and survivors. The Office of Cancer Survivorship[352] addresses the physical, psychosocial, and economic impacts of cancer diagnosis and cancer treatment as well as the need for interventions to promote positive outcomes in survivors and their families. Important early findings suggest long latencies for treatment-related effects and highlight the need for extended follow-up, early identification, and intervention before complications become more serious.

[348] http://appliedresearch.cancer.gov/areas/assessment/comwg.html.
[349] http://outcomes.cancer.gov/cancors/.
[350] http://appliedresearch.cancer.gov/poc/.
[351] http://ncccp.cancer.gov/.
[352] http://dccps.nci.nih.gov/ocs/office-survivorship.html.

To improve the outcomes of cancer patients, advances in knowledge must be effectively disseminated to the public and to health care providers. The Cancer Control P.L.A.N.E.T.[353] Internet-based portal is a collaborative effort aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers to design, implement, and evaluate evidence-based cancer control programs. P.L.A.N.E.T. assists local programs with resources that help them determine cancer risk and burden within their state and helps states identify potential partners. P.L.A.N.E.T. also provides online resources for interpreting research findings and recommendations and for accessing products and guidelines for planning and evaluation.

Due in part to an explosion of information through a number of communication channels—including health information in the news media, where cancer consistently ranks first among disease-specific news coverage—the public may at times hear conflicting or confusing information regarding cancer prevention recommendations and other health information. Health communication is a rapidly evolving field. To monitor changes and trends in health and cancer communication, NCI developed the Health Information National Trends Survey a decade ago[354] to examine how different communication channels, including the Internet, are used by adults 18 years and older to obtain vital health information for themselves and their loved ones. Program planners use the data to address barriers to effective health information usage across populations and create more effective communication strategies. Finally, social scientists use the data to study health communication in the information age in order to recommend strategies for reducing the burden of cancer throughout the population.

NCI also invests in research to elucidate the factors that contribute to cancer health disparities. The Basic Research in Cancer Health Disparities initiative supports research to understand the biological mechanisms for cancer disparities among various racial and ethnic populations. The program investigates genetic/biological differences and cellular mechanisms that may lead to cancer disparities among various populations. The Centers for Population Health and Health Disparities program[355] supports transdisciplinary research involving social, behavioral, biological, and genetic studies to elucidate the causes of health disparities and devise effective methods of preventing, diagnosing, and treating disease and promoting health. Using a regional approach, the Geographical Management of Cancer Health Disparities Program[356] is working to support biospecimen collection, development of bioinformatics platforms, clinical trials recruitment and retention, emerging technologies applications, and the development of research projects that focus on health disparities in racial/ethnic minority and underserved communities. As part of a broader Center to Reduce Cancer Health Disparities Biospecimen Awareness/Education and Collection Campaign, the Geographical Management of Cancer Health Disparities Program also is working to raise awareness about the importance of biospecimens and to educate minority populations about biospecimen research. Working in collaboration with TCGA, this national campaign aims to increase the collection of high-quality breast and prostate cancer specimens from racial/ethnic minority and underserved populations as well as raise awareness and education about biospecimen research.

The RAS Initiative[357] is a targeted plan to develop therapeutic strategies against cancers driven by one of the most mutated genes in all of cancer, *KRAS*. Mutations in *KRAS* are especially prevalent in pancreatic, lung, and colorectal cancers. This national mission was developed during FY 2013 as a result of consultation with cancer researchers, clinicians, and drug developers and was approved by the National Cancer Advisory Board and NCI's Board of Scientific Advisors in June 2013. The program operates on a hub-and-spoke model, with hub research ongoing at the Frederick National Laboratory for Cancer Research (FNLCR), the only Federally Funded Research and Development Center in HHS. The researchers at FNLCR reach out and collaborate with pharmaceutical companies, academic institutions, and NCI intramural researchers as well as other government entities. Five main projects have been developed during FY 2013 and research began in FY 2014. The goals of the RAS Program are to better understand the role of *RAS* mutations in cancer in order to

[353] http://cancercontrolplanet.cancer.gov/.
[354] http://hints.cancer.gov/.
[355] http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html.
[356] http://crchd.cancer.gov/inp/gmap-overview.html.
[357] http://www.cancer.gov/researchandfunding/priorities/ras.

solve the challenges of treating *RAS*-driven cancers and to build an open model of collaboration among government, academic, and industry researchers that will re-energize efforts to develop *RAS* therapeutics.

The incidence of cancer in LMIC is projected to increase in the coming years. It is estimated that approximately 70 percent of cancer deaths will occur in LMIC. A high prevalence of cancer risk factors, such as smoking, an unhealthy diet, and infections, are contributing to this increase, as are improvements in infectious disease management, health care delivery, and sanitation, which have augmented population longevity. The NCI Center for Global Health[358] was launched in 2011 to support NCI's goal to advance cancer research, build expertise, and leverage resources across nations. The Center focuses on reducing the global burden of cancer by supporting research programs and activities in cancer prevention, screening and early detection, diagnosis, treatment, palliation, and survivorship. The Center builds capacity for cancer research in the U.S. and other countries through training and education as well as through research cooperation with other countries. For example, the Center has offices in other countries, including India, Argentina, and Belgium, and has established research networks in Latin America, the Caribbean, and Ireland.

Cancer Research Infrastructure and Workforce

The infrastructure required for initiating and sustaining a robust, multifront effort to advance the science and treatment of cancer is exceptionally complex and varied in terms of its components. One such component is technology; NIH places a high priority on technology development to support both research and the application of research findings to improve health care delivery, emphasizing the areas of bioinformatics, cancer imaging, proteomics, and nanotechnology. As NIH-supported scientists begin to apply new discoveries to cancer prevention, early detection, and treatment, it will be important to integrate the tools and insights of research, science, and technology as effectively as possible.

[358] http://www.cancer.gov/aboutnci/globalhealth.

NCI's Center for Biomedical Informatics and Information Technology[231] (CBIIT) administers the National Cancer Informatics Program[232] (NCIP), which supports the informatics requirements and research priorities of the intramural and extramural programs of NCI divisions, offices, and centers (see the section on "Harnessing Technology" in Chapter 2 for more details). In the cancer biology and genomics domain, CBIIT and NCIP program staff work closely with the Center for Cancer Genomics to make the large data sets generated by The Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and the Cancer Target Discovery and Development (CTD2) programs, among others, accessible to the cancer research community.

Spanning translational and clinical research, CBIIT staff work with members of the Cancer Imaging Program to support the research of the Quantitative Imaging Network (QIN). The network comprises academic centers that (1) share imaging data and metadata produced by current commercial imaging platforms; (2) integrate these data types with clinical data; and (3) put the data to secondary use. CBIIT staff also collaborate with the Cancer Therapy Evaluation Program to support the standardization of data annotations to facilitate the sharing of information from NCI-supported clinical trials through the Clinical Trials Reporting Program.

Research workforce development is critical to maintaining and enhancing the nationwide (as well as global) infrastructure for cancer research. NCI supports training within IRP and through training awards to institutions and individuals in the extramural community. NIH will continue to invest in attracting the best and brightest graduate students and postdoctoral fellows—including those from populations underrepresented in biomedical research—for example, through the Continuing Umbrella of Research Experiences diversity training program.[359] The program is a comprehensive, holistic training approach that provides funded training and career development opportunities, as well as mentoring, for high school, pre- and post-doctoral students, and early stage investigators from backgrounds typically underrepresented in biomedical research, helping them to become productive, independent cancer and cancer health disparities research investigators and

[359] http://crchd.cancer.gov/training/cure-overview.html.

clinician-scientists. NCI also supports junior faculty researchers from underrepresented populations in an effort to promote workforce diversity in the cancer research community.

Additionally, NCI supports training in a number of other disciplines. TPS-ON provides training and professional development opportunities for researchers at all career stages, with the aim of cultivating a workforce capable of working at the interface of the physical sciences and cancer biology. The Alliance for Nanotechnology in Cancer program's Cancer Nanotechnology Training Centers are focused on educating and training researchers from diverse fields in the use of nanotechnology-based approaches to advance cancer research. The Interagency Oncology Taskforce, a partnership with FDA, is designed to train scientists in cancer-related scientific research and research-related regulatory review, policies, and regulations. The Cancer Prevention Fellowship Program provides a strong foundation for scientists and clinicians to train in the field of cancer prevention and control, with opportunities for cutting-edge research in the basic, quantitative, and social and behavioral sciences, and a partnership between NCI and FDA provides opportunities for prevention research in drugs, biologics, and medical devices. Finally, NCI also offers support to investigators interested in translational and clinical research. The SPORE Career Development Programs support investigators who want to develop or refocus their careers on translational cancer research in specific organ-site malignancies. The Cancer Clinical Investigator Team Leadership awards provide two years of funding to exceptional mid-level clinical investigators who lead NCI-sponsored clinical trials but are not principal investigators at NCI-designated Cancer Centers.

Conclusion—Realizing the Vision of Precision Medicine

Through both extramural and intramural initiatives, NIH is progressively realizing its vision of precision medicine and care for all those who are affected by cancer. With sustained, robust public support, NIH will continue to make critical advances in the effort to reduce the morbidity and mortality associated with the second leading cause of death among American adults.

Neuroscience

Neurological disorders and mental illness take an enormous toll on human health and the economy. Even rare disorders carry a substantial collective burden, as they often have an early onset and long duration, and the stigma commonly attached to neurological and mental disorders further compounds individual and societal impact. According to 2005 estimates, neurological disorders strike more than 1 billion people worldwide, accounting for 12 percent of total deaths.[360] In the U.S., this includes approximately 100 million adults who suffer from chronic pain,[361] an estimated 10 percent or more adults who experience migraine headaches,[362] 2.3 million adults with epilepsy,[363] and as many as 5.1 million adults with Alzheimer's disease (AD),[364, 365] to name a few. One in seven U.S. adults aged 72 and older has dementia, and current demographic trends project a growing burden from age-related diseases of the nervous system as populations benefit from increased longevity. For example, the number of people with AD is expected to rise to as many as 13.8 million by 2050 unless effective interventions are developed.[366] The cost of caring for people with AD and dementia was as high as $215 billion in 2010.[367]

Other neurological disorders are costly as well. Stroke is the fourth leading killer of adults in the U.S. and a major cause of long-term disability. An estimated 6.8 million Americans have had a stroke, with annual medical and disability costs totaling more than $36.5 billion and estimated to triple by 2030.[368] Traumatic brain injury (TBI) is the leading cause of death and long-term disability in young adults,[369] with direct and indirect costs of severe TBI reaching approximately $76.5 billion in 2010.[370] Each year, 2.5 million Americans

[360] http://www.who.int/mediacentre/news/releases/2007/pr04/en/index.html.
[361] Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, D.C.: Institute of Medicine, 2011. Available at: http://iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx.
[362] WHO. Atlas of Headache Disorders and Resources in the World 2011. 2011. Available at: http://www.who.int/mental_health/management/atlas_headache_disorders/en/.
[363] CDC. *MMWR Morb Mortal Wkly Rep*. 2012;61(45):909–13. PMID: 23151949.
[364] Plassman BL, et al. *Neuroepidemiology*. 2007;29:125–32. PMID: 17975326.
[365] Hebert LE, et al. *Arch Neurol*. 2003;60:1119–22. PMID: 12925369.
[366] Hebert LE, et al. *Neurology*. 2013;80(19): 1778–83. PMID: 23390181.
[367] Hurd MD, et al. *New Engl J Med*. 2013; 368(14): 1326–1334. PMID: 23550670.
[368] Go AD, et al. *Circulation*. 2014;129:e28–e292. PMID: 24352519.
[369] http://www.cdc.gov/traumaticbraininjury/get_the_facts.html.
[370] http://www.cdc.gov/traumaticbraininjury/severe.html.

visit emergency departments or are hospitalized from TBI, and many others with mild TBI do not seek emergency care. Head injury also accounts for an estimated 20 percent of combat-related injuries in modern wars, and blasts are a leading cause of TBI in military personnel.[371]

In 2012, an estimated 9.6 million adults in the U.S. aged 18 or older had a serious mental illness within the past year; this represented 4.1 percent of all U.S. adults.[372] Mental disorders result in more disability for U.S. adults than any other class of medical illness,[373] and a conservative estimate places the total direct and indirect annual costs of mental illness at more than $300 billion.[374] In addition, the lifetime prevalence for any mental disorder in youth aged 13–18 is 46 percent; and the lifetime prevalence of "severe" mental disorders in youth is 21 percent.[375]

In 2012, among persons in the U.S. aged 12 or older, 17.3 million were classified with dependence on or abuse of alcohol, and 6.9 million with dependence on or abuse of illicit drugs.[376] The overall social and economic burden of substance abuse continues to rise, with annual costs related to alcohol, tobacco, and illicit drug abuse totaling more than $600 billion.[377, 378, 379]

[371] Ling G, et al. *J Neurotrauma*. 2009;26(6):815–25. PMID: 19397423.
[372] Substance Abuse and Mental Health Services Administration (SAMHSA). Results from the 2012 National Survey on Drug Use and Health: Mental Health Findings, NSDUH Series H-47, HHS Publication No. (SMA) 13-4805 (2013). Rockville, MD: Substance Abuse and Mental Health Services Administration. Available at: http://www.samhsa.gov/data/NSDUH/2k12MH_FindingsandDetTables/2K12MHF/NSDUHmhfr2012.htm.
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[377] Rehm J, et al. *Lancet*. 2009;373(9682):2223–33. PMID: 19560604.
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[379] National Drug Intelligence Center. The Economic Impact of Illicit Drug Use on American Society. Washington D.C.: United States Department of Justice, 2011. Product No. 2011-Q317-002. Available at: https://www.justice.gov/archive/ndic/pubs44/44731/44731p.pdf.

NIH Funding for Neuroscience and Disorders of the Nervous System

NIH funding for research in neuroscience and disorders of the nervous system was $5,618 million in FY 2012, and $5,340 million in FY 2013 appropriations.[380]

Summary of NIH Activities

Composed of the brain, spinal cord, sensory organs, and nerves of the body, the nervous system underlies perception, movement, emotions, learning, and memory as well as other functions essential to individual and societal well-being. The nervous system interacts with all other organ systems and is affected by countless diseases, conditions, and environmental factors. Moreover, with limited capacity for self-repair, the nervous system is particularly vulnerable to damage from injury or infection, and its repair mechanisms are poorly understood. Neuroscience research includes (1) basic science studies to understand the nervous system and its functions and (2) translational and clinical research to develop interventions to prevent and treat diseases and conditions affecting the nervous system, which include a broad range of neurological disorders; disorders affecting cognitive, emotional, and behavioral function; diseases and conditions that impair the primary senses; and developmental and age-related disorders. Given the intrinsic complexity of the nervous system and its central role in physiology and behavior, neuroscience research spans many disciplines—from genetics to physiology to psychology—and applies tools from such areas as molecular biology, anatomy, computer science, and imaging technologies.

The intramural and extramural programs of several ICs have a major focus on the nervous system, but the full scope of NIH neuroscience activities extends to components of research portfolios across most of the Agency, reflecting the multidisciplinary nature of the field and the importance of the nervous system to many aspects of human health, development, and disease. These activities often involve collaborative efforts combining the unique strengths and expertise of individual ICs. To reinforce such collaborations, NIH established the Blueprint for Neuroscience Research,

[380] http://report.nih.gov/categorical_spending.aspx.

which accelerates neuroscience research through training programs, the development of shared tools and resources, and initiatives to address challenges in neuroscience that transcend the mission of any single IC.

NIH research on neurological diseases, largely supported by NINDS, seeks to uncover their causes and mechanisms and to develop drugs and other treatments or preventive strategies. Neurological disorders include common killers and major causes of disability (e.g., stroke, TBI, multiple sclerosis, epilepsy) as well as hundreds of less common diseases (e.g., lysosomal storage disorders, spinal muscular atrophy, muscular dystrophies, inherited neuropathies, neurofibromatosis, tuberous sclerosis, Rett syndrome, Tourette syndrome). Many neurological disorders have genetic or developmental origins. Others result from trauma to the nerves, spinal cord, or brain; from autoimmune, infectious, or systemic disease; from tumor growth in nervous system tissues; or from neurodegenerative processes, as in Parkinson's disease (PD), glaucoma, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). Still others result from, or are suspected of resulting from, environmental exposure to certain substances, such as metals, pesticides, polychlorinated biphenyls, and solvents.

Brain disorders that affect cognitive, emotional, and behavioral function include schizophrenia and psychoses; Autism Spectrum Disorder (ASD) and other developmental disorders; attention deficit hyperactivity disorder (ADHD); mood and anxiety disorders; post-traumatic stress disorder (PTSD); eating disorders; and addiction to nicotine, alcohol, and other substances, among others. Through research efforts led by NIAAA, NICHD, NIDA, NIEHS, NIMH, and other ICs, NIH focuses on understanding the causes of these conditions (e.g., the underlying neural and behavioral bases) and their effects (e.g., the acute and long-term effects of substance abuse and dependence on the nervous system) so as to develop effective therapies and interventions for treatment and prevention.

Communication disorders can make it challenging for a person to sense, interpret, and respond to environmental stimuli. Not only do communication disorders compromise a person's physical health, but they also affect that person's emotional, social, recreational, educational, and vocational life. For example, one such disorder, aphasia, results from damage to portions of the brain that are responsible for language. These heterogeneous disorders usually occur suddenly, often as the result of a stroke or head injury, but they may also develop slowly, as in the case of a brain tumor, an infection, or dementia. NIDCD, NINDS, NICHD, NIMH, and NIA support research on these disorders. The goal of this research is to develop therapies to improve an individual's ability to communicate by helping the person use his or her remaining capabilities, to restore language abilities as much as possible, to compensate for language problems, and to learn other methods of communicating.

NEI funds research on basic visual neuroscience in the eye and brain and on diseases and conditions that affect vision. NIDCD conducts and supports biomedical and behavioral research, as well as research training in the normal and disordered processes of hearing, balance, taste, smell, voice, speech, and language related to answering fundamental scientific questions and to prevent, screen, diagnose, and treat human communication–related disorders. And NIA supports basic and clinical research on sensory and motor changes that occur as a result of advancing age.

NIH-supported research also studies the many ways the nervous system interacts with and regulates changes in the body's internal environment. This research, including efforts supported by NHLBI, NIA, and NIDDK, focuses on such areas as circadian rhythms and sleep disorders; neuroendocrine processes that regulate or respond to stress, hormone levels, and motivational states; and the neural basis of appetite and feeding, which is of key relevance to slowing the increasing rates of obesity worldwide.

Nervous system disorders may arise during early development, strike young adults, or emerge late in life. NICHD, NIEHS, and other ICs sponsor research on the development of the nervous system and its functions. This research encompasses studies of structural birth defects, including spina bifida and other neural tube defects; associated conditions, such as hydrocephalus, cerebral palsy, and Down syndrome; and other causes of intellectual and learning disabilities. Nervous system development in humans continues into early adulthood, and developmental

processes and external influences contribute to mental fitness and disease risk later in life, including the risk for addiction, which often begins in childhood or adolescence. At the other end of the lifespan, with key support from NIA, NINDS, and NIEHS, NIH research on the aging nervous system includes studies of age-related disorders, such as AD and other dementias, as well as environmental and lifestyle factors affecting brain, cognitive, and emotional health in aging populations. Because individuals with Down syndrome are predisposed to early onset AD, NIA and NICHD has developed initiatives to identify early AD markers in people with Down syndrome, which may enhance our understanding of AD in the general population as well.

Across all ages, the nervous system is a common target of exposure to toxins, pollutants, metals, food ingredients, and other agents, the effects of which range from acute reactions to developmental disruption to neurodegeneration. NIH-sponsored research on the consequences of such environmental exposures for nervous system development, function, and disease is a particular focus of NIEHS, including the Centers for Neurodegeneration Sciences, an initiative focused on integrating basic and clinical research on the environmental and genetic interactions that contribute to PD and related neurodegenerative diseases.

NIH also supports collaborative research and capacity-building projects on nervous system disorders from a global point of view. The Brain Disorders in the Developing World: Research Across the Lifespan program, led by FIC, supports innovative neuroscience-related research and research training projects in LMIC that contribute to the long-term goal of building sustainable research capacity in nervous system function and impairment throughout life.

Neurodevelopment, neuroplasticity, and neurodegeneration are common themes that reflect shared biological processes found in many aspects of nervous system function and disease. The remainder of this section will highlight selected examples of activities and progress in NIH-enabled neuroscience research across different ICs as well as challenges and future opportunities. Additional activities and initiatives will exemplify how collaborative approaches are facilitating advances in basic, translational, and clinical neuroscience.

Research activities relevant to neuroscience and disorders and conditions affecting the nervous system are also described in other sections of this report. For example, for information on NIH research on stroke and chronic pain, see the section "Chronic Disease and Organ Systems" in this chapter. Similarly, see the section "Life Stages, Human Development, and Rehabilitation" in this chapter for more information about research on certain neurodevelopmental and age-related disorders as well as additional information on neuroprosthetics research.

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Complex interactions between gene expression and function, endocrine and other physiological processes, neuronal activity, and external influences guide the development of the nervous system. From the early differentiation of its many neuronal and other cell types to the establishment of billions of connections between neurons, each step in nervous system development is vulnerable to disruption by disease, injury, or environmental exposures. NIH research across all stages of neurodevelopment is leading to a better understanding of neurological, mental, and behavioral function in health and disease throughout life, as well as to new treatments and preventive strategies.

How is it that a person's blood cells and brain cells contain the same DNA within them, yet look different, have different proteins, and serve such obviously different functions? How can the identical genome create such diversity? The answer is that only a fraction of the genome's DNA is expressed in any given cell, and the specific genes that are expressed define the cell's identity: one pattern defining blood cells and another pattern defining brain cells. The main translator between DNA and protein is RNA. Every cell type has a distinct RNA profile—called its transcriptome. Supported by NIMH funding from the American Recovery and Reinvestment Act, a consortium of investigators from the Allen Institute for Brain Science, the University of Southern California, and Yale University is creating an atlas of the brain's transcriptome in a project called BrainSpan.[381] BrainSpan represents a map of how

[381] http://www.brainspan.org.

the genome is translated throughout the development of the human brain. The investigators have made a key finding: The gene expression pattern in the fetal brain differs so greatly from the pattern observed in the adult brain that the fetal brain could almost be considered a different organ. Moreover, BrainSpan researchers have aligned particular aspects of the fetal brain transcriptome with risks for schizophrenia. These findings underscore the importance of studying the developing brain in order to understand neuropsychiatric disorders.[382]

Developmental disability is a severe, long-term disability that can affect cognitive ability, physical functioning, or both. According to CDC, an estimated 37 million–53 million people in the U.S. have physical and mental disabilities.[383] The Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers support projects that address cerebral connectivity; genetics and environmental influences on brain development; efforts to prevent and treat conditions ranging from brain injury in premature infants to ASD; and research programs in genetic/genomic disorders, inborn errors of metabolism, and mitochondrial disorders. In addition, through its Hunter Kelly Newborn Screening Research Program, NIH is supporting the development of technologies and therapies for newborn screening and for screenable disorders as well as providing an infrastructure to support newborn screening research. The goals are to develop fast, reliable, and cost-effective means to screen newborns and to expand the number of conditions these tests can assess. Such screening makes it possible to begin treatment early, when chances for success are greatest.

Other Institutes also support research on brain development and neurodevelopmental disorders. For example, extremely low gestational age neonates (ELGANs) born before 28 weeks of gestation are at high risk for death or moderate-to-severe neurodevelopmental impairment. The Preterm Epo Neuroprotection Trial supported by NINDS seeks to determine whether neonatal treatment with recombinant erythropoietin (Epo) will decrease early mortality and neurodevelopmental disability in ELGANs, as measured at two years of age. Epo is a widely available drug with promising neuroprotective properties, and it has been used safely in neonates to stimulate red blood cell production. NINDS also funds an ongoing study to identify markers that may indicate which ELGANs are at most risk for long-term neurological deficits, which could facilitate early intervention.

NINDS-supported research on Down syndrome includes (1) studies in mouse models to determine which of the genes triplicated in Down syndrome are responsible for cognitive deficits and (2) a milestone-driven small business research project to develop a drug therapy to improve cognitive function in people with the disorder. NIH's establishment of a new Down syndrome registry, for which the plan was supported by the public-private Down Syndrome Consortium, will enable people with Down syndrome and family members to enter contact information and health history in an online, secure, confidential database. Registry participants will be able to customize and update their information and choose which information they would like to display, including reminders about their own medical care. Ultimately, the repository will be able to link biorepositories to tissue samples and other resources, with a goal of making it easier for patients to take part in clinical studies for new medications and other treatments for Down syndrome.

Prenatal alcohol exposure is the leading preventable cause of birth defects and developmental disorders in the U.S. In a study supported by NIAAA, NIDA, and NICHD, researchers found that brain growth and remodeling observed during normal development was disrupted in the brains of children who were heavily exposed to alcohol in utero, compared to unexposed children. The finding suggests that heavy alcohol exposure during gestation may have long-term effects on brain maturation; however, environmental influences during childhood also may play a role in the developmental trajectory of prenatally exposed children.[384]

Both genetic and environmental factors influence nervous system development and function, and a growing area of neuroscience research focuses on how genes and the environment interact to influence both disease course and treatment for a range of disorders, including multiple sclerosis, PD, depression and other mood and anxiety disorders, addiction, and ASD.

[382] Gulsuner S, et al. *Cell*. 2013;154(3):518–29. PMID: 23911319.

[383] http://www.cdc.gov/features/ada-anniversary/index.html. Note that this source estimates the total number of people with physical and/or mental disabilities, but does not distinguish the subset of those with developmental disabilities.

[384] Lebel C. et al. *J Neurosci*. 2012;32(44):15243–51. PMID: 23115162.

ASD is a complex neurological disorder that affects children and adults with varying degrees of severity. Although ASD is characterized by challenges in three core domains of functioning (social impairments; communication difficulties; and restricted, repetitive, or stereotyped patterns of behavior), considerable variability exists between individuals with autism spectrum disorder in these and other clinical features, suggesting the contribution of multiple developmental trajectories and causal factors. To better understand the complexity of ASD, NIH supports research on the potential causes of the disorder, including inherited or spontaneous alterations in specific genes, exposures to environmental risks or hazards, or a combination of both genetic and environmental risk factors. ASD research activities are coordinated across NIH through the NIH Autism Coordinating Committee (NIH ACC), which includes participation from seven ICs.[385] The NIH ACC also closely follows the activities of the federal Interagency Autism Coordinating Committee (IACC) and, in particular, works to ensure that research objectives—designated in the IACC *Strategic Plan for Autism Spectrum Disorder Research*—are met as they apply to the missions of the NIH Institutes, including objectives targeting research on the possible genetic and environmental etiology of autism.[386]

In 2012, a consortium of investigators supported by NIH identified spontaneous genetic mutations that were highly associated with familial risk of ASD. Moreover, fathers were four times more likely than mothers to transfer these specific genetic mutations to offspring, and the number of these genetic mutations was higher among older fathers.[387] These spontaneous mutations may reflect cumulative environmental exposure as a father ages. NIH Institutes also have collaborated to support large research initiatives such as the Early Autism Risk Longitudinal Investigation study. Supported by NIEHS, NICHD, NIMH, and NINDS, the study examines risk factors in mothers of children with ASD at the start of a new pregnancy, documenting the development of the newborn siblings through age three.

In mid-2013, NIH-funded researchers discovered that people with disorders traditionally thought to be distinct—ADHD, ASD, bipolar disorder, major depression, and schizophrenia—were more likely to have suspect genetic variation at the same four chromosomal sites,[388] including risk versions of two genes that regulate the flow of calcium into cells. Evidence for such genetic overlap previously had been limited to pairs of disorders. Another team of researchers, funded by NIMH, found that early signs of autism can be detected in 6-month-old infants.[389] Thus, some of the first signs of ASD, such as limited visual attention to social scenes, can be detected very early in development, well before the emergence of diagnostic features. Although it may be too soon to push the age of diagnosis down to the first year of life, the study suggests an important direction for further research as well as a tremendous window of opportunity to intervene.

Shifting from research on early intervention to overall health outcomes, in FY 2012 NIMH funded the Study of Health Outcomes in Children with ASD and Their Families, a two-year project to explore the use of existing administrative data to further our understanding of ASD, including variables related to health outcomes, and the use of health care by children with ASD and their families. Initial findings from the study show that a valid ASD diagnosis can be derived from a health insurance claims database. The study has identified 33,000 individuals with ASD, nearly 100,000 of their family members, and more than 100,000 controls. Children with ASD and their siblings had higher rates of co-occurring health conditions than respective comparison groups. Children with ASD and their families use health care services at higher rates than children and families who are not affected by ASD. Younger siblings of children with ASD have a lower vaccination rate than younger siblings of controls.[390]

The human brain continues to mature into early adulthood, and understanding normal nervous system development is essential to knowing when, where, and how developmental processes can go wrong. An improved understanding of the normal course of human brain development is also yielding insights into behavioral and cognitive development and function across the lifespan. For example, previous brain

[385] The seven NIH ACC Institutes and Centers are NCCAM, NICHD, NIDCD, NIEHS, NIMH, NINDS, and NINR. Representatives from NIAID participate in NIH ACC meetings as well.
[386] http://iacc.hhs.gov/strategic-plan/2013/index.shtml.
[387] O'Roak BJ, et al. *Nature*. 2012;485(7397):246–50. PMID: 22495309
[388] http://www.nimh.nih.gov/news/science-news/2013/five-major-mental-disorders-share-genetic-roots.shtml.
[389] http://www.nimh.nih.gov/news/science-news/2013/precursor-symptoms-to-autism-detected-in-6-month-old-infants.shtml.
[390] http://iacc.hhs.gov/events/2013/slides_anjali_jain_012913.pdf.

imaging studies have shown that one of the last brain areas to fully mature is the prefrontal cortex, an area important for decision-making and impulse control. This aspect of brain development may contribute to impulsive behavior in teenagers and help explain their increased susceptibility to substance abuse and addiction.

A number of human and animal studies have suggested that the developing brain is vulnerable to heavy alcohol use in adolescence. NIAAA's National Consortium on Alcohol and Neurodevelopment in Adolescence, a longitudinal study of 800 youth ages 12–21, was launched in FY 2012 to elucidate the short- and long-term effects of alcohol exposure on the developing adolescent brain and to identify brain characteristics and/or changes that may predict risk for developing alcohol use disorders.

NIH investigators already are using knowledge about human brain and behavioral development to guide research on interventions to treat nervous system disorders or to reduce their risk of occurrence later in life. For example, researchers reporting delayed development of the prefrontal cortex in ADHD are now studying the effects of ADHD treatment on the rate of cortical maturation. Research has established that substance abuse is a developmental disease beginning in childhood and adolescence. Therefore, prevention strategies must focus on developmentally appropriate interventions for youth. In fact, universal prevention approaches that teach all children (regardless of risk) problem-solving, refusal, and coping skills have proven successful, not just in reducing future drug abuse risk but also other related risk behaviors. The NIAAA Underage Drinking Initiative similarly supports research on the risk factors associated with underage drinking as well as efforts to develop and implement effective interventions within a developmental framework.

Neuroplasticity: Substrates for Change and Repair

Throughout development, and even after basic structure and circuitry have been established, the nervous system retains a remarkable capacity to adapt to changes in the body's internal environment and external conditions and events. This capacity, known as plasticity, reshapes the function and activity of neuronal networks, and it occurs at many levels of the nervous system. Plasticity enables beneficial adaptations, generally associated with a gain in function, including acquiring new knowledge, improving performance, and adjusting behavior. However, neuroplasticity can also lead to maladaptive changes associated with negative consequences, which contribute to a range of conditions, including mood disorders, addiction, chronic pain, and cognitive impairment. Neuroplastic changes also are intrinsically connected to biological events such as neurogenesis, neurodegeneration, neuronal sprouting, and changes in signal transduction pathways, which all play a role in several neurological disorders. Maladaptive plasticity can also arise as a consequence of long-term drug exposure, as in cases of drug abuse and levodopa-induced uncontrolled movements (dyskinesias) in patients with PD. By better understanding the underlying mechanisms of neuroplastic changes in the nervous system, researchers may be able to harness their therapeutic potential and limit their deleterious consequences.

Plasticity-related processes in brain circuits contribute to many of the underlying causes of epilepsy, which include developmental malformations; genetic mutations; trauma, such as stroke or head injury; brain tumor; and central nervous system (CNS) infection and inflammation. In April 2013, NINDS hosted "*Curing the Epilepsies 2013: Pathways Forward*," the third in a series of *Curing the Epilepsies* conferences held in partnership with epilepsy advocacy and professional organizations. These conferences have led to the development of *Benchmarks for Epilepsy Research*, which reflect priorities shared across the epilepsy community for research toward clinically meaningful advances in understanding and treating the epilepsies. With input received during and before the conference, NINDS developed the 2014 *Benchmarks for Epilepsy Research* as a framework for focusing research and tracking progress over the next 5–10 years.[391] A range of comorbid conditions beyond seizures can affect people with epilepsy, including depression, cognitive and behavioral impairments, and neurodevelopmental disorders such as ASD and intellectual disabilities. Among other updates, the 2014 Benchmarks

[391] http://www.ninds.nih.gov/research/epilepsyweb/2014benchmarks.htm.

will encourage the integration of research on epilepsy comorbidities into epilepsy research as a whole to reflect the complex relationships these conditions have with epilepsy and seizures, underlying disease mechanisms, and effects of epilepsy treatment.

One way NINDS is working to facilitate research outlined by the Benchmarks is through the Epilepsy Centers without Walls program, which supports research by multidisciplinary consortia to solve specific challenges in the prevention, diagnosis, or treatment of epilepsy. The first center to launch, known as the Epi4K Consortium, has focused on identifying genetic contributors to more common forms of epilepsy by analyzing the genomes of 4,000 epilepsy patients and families collected by several major research groups across the world.[392] Already, the Epi4K Consortium has found new gene mutations associated with infantile spasms and Lennox-Gastaut syndrome, severe forms of childhood-onset epilepsy that are difficult to treat and are associated with intellectual and developmental disabilities.[393] Interestingly, the identified genes showed substantial interconnections with genes and gene networks previously linked to intellectual disability and ASD. NINDS also has supported planning grants in advance of potential Centers without Walls to address additional challenges in epilepsy research, including Sudden Unexpected Death in Epilepsy, which occurs at a higher rate than sudden death in the general population, and the development of treatments to prevent epilepsy or modify the course of disease.

Mental disorders are associated with functional changes in highly plastic brain areas that play a key role in cognition, complex decision-making, and impulse control. Harnessing this inherent plasticity holds promise for the development of more precisely tailored interventions. For example, antidepressant or cognitive behavioral therapies for major depression generally require six to eight weeks to have an effect. NIMH is funding research on next generation antidepressants, which have been shown to reduce depression, including thoughts of suicide, within six hours, with effects persisting in many cases for up to a week after a single intravenous infusion. In addition, the Rapidly-Acting Treatments for Treatment-Resistant Depression initiative is leveraging the development of rapidly-acting treatments for severe, treatment-resistant depression. The initiative is establishing a small team of sites that will focus on identifying and testing promising pharmacological and/or nonpharmacological interventions that produce a substantial antidepressant effect within 72 hours of initial administration. The initiative also aims to conduct randomized clinical trials that test these promising interventions in adult patients diagnosed with treatment-resistant depression.

Neuroplasticity also underlies a range of changes in brain function and behavior involved in the development and persistence of addiction. For example, a recent study conducted by NIAAA intramural investigators demonstrated that chronic alcohol exposure in mice results in brain adaptations that shift behavior control away from the prefrontal cortex toward the dorsal striatum, a region of the brain associated with motivation and habit formation. This finding provides a biological mechanism that may help explain the progression of alcohol use disorders.[394]

While opioid analgesics are currently the most powerful medications on the market for chronic pain, frequent use of these drugs can cause plastic changes in the nervous system that put patients at risk, making them vulnerable to addiction, tolerance, and physical dependence. This risk limits the drugs' long-term treatment value. Scientists are working toward the development of a morphine-like drug that will have the analgesic qualities of morphine, but without the drug's negative side effects. Another focus of NIH-supported research to develop new pain treatments is the cannabinoid signaling system. Just as the brain produces natural opioid-like compounds, it also produces natural compounds that act on the same receptors as the neuroactive component in the cannabis plant (marijuana). Cannabinoid signaling modulates neuronal activity and plasticity and also plays a role in modulating pain. Research suggests that selective activation of cannabinoid signaling pathways may provide pain relief with minimal mind-altering effects.

Maladaptive nervous system plasticity has been recognized as the underpinning of the chronicity of many pain disorders, and mechanisms of these changes are the focus of much NIH-supported research. For example, through

[392] http://www.epi4k.org/epi4k-consortium/.
[393] Epi4K Consortium, et al. *Nature*. 2013 Sep 12;501(7466):217–21. PMID: 23934111.
[394] DePoy L, et al. *Proc Natl Acad Sci U S A*. 2013 Sep 3;110(36):14783–8. PMID: 23959891.

NIH support, researchers are exploring the role of increased activity of neurotransmitters in enhancing neuronal activity in response to pain as well as changes in functional connections among pain-related neural circuits. NIH-funded research also has demonstrated the role of increased activity in certain brain structures in amplifying pain signals or causing or maintaining persistent pain. An important area of research has shown that changes in cortical brain circuits of people with acute low back pain can predict who is likely to recover and who is likely to develop chronic back pain even though the injuries are similar.[395]

NIH-supported researchers have also reported new findings on the mechanisms that lead to neuropathic pain induced by nerve injury or disease. Following injury, the nervous system undergoes a tremendous reorganization. Thus, therapies directed at preventing these long-term changes may prevent the development of chronic pain conditions. Most available treatments for neuropathic pain target neurons, and some approaches are being developed to deliver therapeutic agents directly to nerves that carry pain signals. In addition, recent findings highlight the role of certain enzymes released by non-neuronal cells called glia, which are involved in immune and inflammatory responses to nerve injury. Ongoing research to develop novel treatments targeting glia may provide a way to halt the maladaptive signaling cascade that results in neuropathic pain and other chronic pain conditions. Preliminary veterinary trials show promise for long-term pain relief with such glia-targeted approaches. NIH also supports efforts to understand how specific drug and nondrug therapies, such as yoga, alter pain-adapted neural networks and thus determine the mechanism of certain therapeutic pain interventions. Future research will focus on whether brain activity profiles measured by brain imaging methods can be used as a biomarker that would allow for an objective diagnosis of different pain conditions and for the prediction of individual responses to specific therapies.

Although plasticity can lead to changes in neural activity patterns throughout life, the adult human brain and spinal cord have limited capacity to replace or repair neurons and long nerve fibers that are lost or damaged by injury or disease. An exciting area of neuroscience research focuses on ways to overcome these limitations and to harness neuroplasticity mechanisms to promote recovery and restore function. For example, spinal cord injury often leads to permanent paralysis and loss of sensation below the site of injury, because damaged nerve fibers are unable to regrow across the injury site. NIH supports research to understand the mechanisms that restrict such regrowth and to design strategies that integrate new nerve fibers into spinal circuitry. A recent NIH-supported study, building on decades of prior research, demonstrated that a combination of intensive training and electrical stimulation of the spinal cord stimulated plasticity in the spinal cord to enable four completely paralyzed individuals to regain some voluntary movement in their legs.[396, 397]

The high rates of TBI in the general population, in athletes, and among military personnel also has increased attention on recovery, rehabilitation, and brain plasticity. Published data on TBI patients suggest that gene polymorphisms related to neuroplasticity may play a role in the variability of recovery. Ongoing TBI research projects supported by NIH are investigating the mechanisms of cognitive, attentional, memory, and motor problems and exploring how plasticity contributes to recovery.

[395] Baliki MN, et al. *Nat Neurosci*. 2012. 15(8): 1117–9. PMID: 22751038.

[396] Harkema S., et al. *Lancet*. 2011;377:1938–47. PMID: 21601270.
[397] Angeli CA, et al. *Brain*. 2014;137:1394–409. PMID: 24713270.

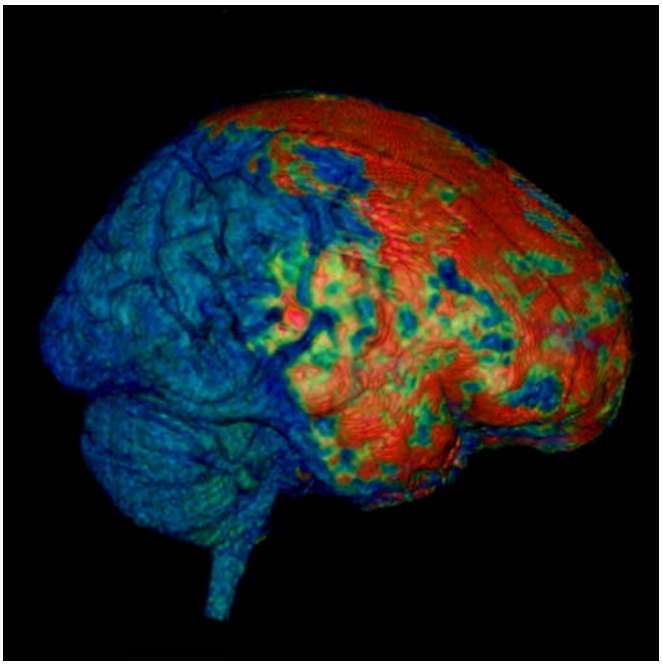


Figure 3-5. *3-D MRI of a human brain reveals injury (in red) to the brain's coverings following mild head trauma. Credit: Lawrence Latour, Ph.D., NINDS.*

Recent advances in TBI research include findings by NINDS intramural researchers who observed the complex cellular responses that occur in response to mild TBI—including the cascade of damage at the vascular, cellular, and molecular levels that spread injury—and the brain's self-protective responses.[398] In addition, the researchers found that an antioxidant could penetrate the brains of mice through the skull and prevent more widespread damage.

Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

The progressive loss of neurons is a common endpoint of many diseases and insults to the nervous system. Such degeneration presents challenges to developing strategies to slow and prevent cell death, protect remaining neurons, and possibly replenish those that are lost. Aging is the most consistent risk factor for many disabling neurodegenerative disorders. As the number of older people in the U.S. is projected to increase dramatically in the coming decades, it is imperative to discover new and more effective ways to improve the health and productivity of this segment of the population.

NIH research on neurodegenerative diseases focuses on understanding their biological and environmental causes, and on efforts to develop interventions that not only alleviate their symptoms, but also may slow or even stop disease progression.

NIEHS has launched an exploratory grant program, Research Linking Environmental Exposure to Neurodegenerative Disease, to spur development of feasibility data for new concepts or adaptation of new technologies, tools, and methods, with an emphasis on establishing the importance of environmental exposure in causing AD, ALS, and PD. A similar program is focused specifically on linking environmental exposures to the development of AD.

AD is the most common cause of dementia in older people, although some inherited forms of the disease become symptomatic in middle age. Although existing treatments can help to manage symptoms in some people, they cannot cure this devastating disease.

President Barack Obama signed the National Alzheimer's Project Act (NAPA) into law on January 4, 2011. NAPA established the National Alzheimer's Plan and requires the HHS Secretary to:

- Create and maintain an integrated national plan to overcome AD and related dementias
- Coordinate research and services across all federal agencies
- Accelerate the development of treatments that prevent, halt, or reverse the disease
- Improve early diagnosis and coordination of care and treatment of the disease
- Improve outcomes for ethnic and racial minority populations at higher risk
- Create an Advisory Council to review and comment on the national plan and its implementation
- Coordinate with international bodies to fight AD globally

Under NAPA, the National Plan to Address AD was released on May 15, 2012, and is updated annually.[399]

NIH, with NIA taking the lead, supports a comprehensive research portfolio on AD, including basic research, epidemiological studies, and clinical trials, to better diagnose, prevent, and treat AD. In response to guidance from NAPA and the National Plan, NIA convened the Alzheimer's Research Summit 2012: Path to Treatment and Prevention to inform the research agenda going forward. Groundbreaking studies are now underway. For example:

- The Alzheimer's Prevention Initiative APOE4 Trial will test two anti-amyloid drugs in cognitively normal older volunteers who are at increased risk of developing late-onset AD because they inherited two copies of the APOE4 allele, the best known genetic risk for late-onset disease. Participants will be assessed through cognitive tests, brain imaging, and cerebrospinal fluid measurements to evaluate whether the drug impacts amyloid, other biological measurements, and the memory and thinking problems related to the disease. The study will test the role of amyloid in the development of AD

[398] Roth TL, et al. *Nature*. 2014;505(7482):223–8. PMID: 24317693.

[399] http://aspe.hhs.gov/daltcp/napa/.

and will, through imaging and biomarker techniques, help identify faster ways to evaluate other promising prevention therapies in the future.

- The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Trial will test the drug solanezumab in 1,000 cognitively normal volunteers, aged 65–85, who have enough of the amyloid protein in the brain, as identified through PET amyloid imaging, to put them at risk for developing AD but do not show clinical symptoms of the disease.
- The Dominantly Inherited Alzheimer's Network Therapeutic Trials Unit will study the effects of different treatments among individuals who are at high genetic risk for developing the disease because they have one of the three genetic mutations for early-onset dominantly inherited AD.

Other ongoing AD research initiatives include:

- A five-year clinical trial to determine if an antibody treatment, crenezumab, designed to bind to and possibly clear away abnormal amounts of amyloid protein in the brains of people with AD, can prevent decline in cognitive function. Crenezumab will be tested among members of a unique and large family population in Colombia who share a genetic mutation known to cause observable signs of AD at around age 45.
- Basic research projects on aging and AD funded by NIA and other Institutes apply directly to understanding the etiology of AD. Major research areas include studies on inflammation, protein quality control, and response to stress. Findings in these domains are likely to shape our approaches at combating AD.
- One hallmark of AD is abnormal deposits of beta-amyloid protein in the brain. These deposits trigger a harmful chain reaction that interrupts the processes that brain cells use to form or maintain connections with each other. NIH neuroscientists, studying visual development and memory formation in the brain, have discovered a protein that could be a missing link in AD progression. This protein may play a similar role in humans, and a drug that blocks this protein might prevent the effects of beta-amyloid deposits in AD.[400]
- Through an initiative within the Common Fund Epigenomics Program, NINDS and NIA funded a large project investigating the role of DNA functional modifications in the cognitive impairment associated with AD.
- The AD Genetics Initiative has facilitated the recent identification of new candidate risk factor genes through GWAS and other high-throughput technologies. This initiative will speed the pace of discovery by providing a centralized resource for investigators to access, study, and share data relevant to AD. NIH-supported investigators are also key partners in the International Genomic Alzheimer's Project, which recently conducted GWAS meta-analyses and identified 11 new susceptibility loci for AD.[401]
- In 2012, NIA and NHGRI established the Alzheimer's Disease Sequencing Project (ADSP). The overarching goals of the ADSP are to (1) identify new genomic variants contributing to increased risk of developing AD, (2) identify new genomic variants contributing to protection against developing AD, and (3) provide insight as to why individuals with known risk factor variants escape from developing AD. ADSP data are expected to be made available to researchers worldwide to boost efforts to identify genomic risk factors for this disease.
- The second iteration of the AD Neuroimaging Initiative (referred to as ADNI2) investigates changes in brain structure and function as people transition from normal cognitive aging to mild cognitive impairment (MCI) to AD. An innovative public-private partnership, ADNI has stimulated the development of more sensitive tools for tracking the development and progression of MCI and AD. Other ADNI projects include a genome-wide association dataset of study participants and a longitudinal study of cerebrospinal fluid samples collected from study participants.
- The AD Translational Initiative for drug discovery and development supports studies leading to the submission of an investigational new drug (IND) application to FDA, a prerequisite for beginning human trials of potential new therapies.

[400] Kim T, et al. *Science*. 2013;341(6152):1399–404. PMID: 24052308.

[401] Lambert JC, et al. *Nat Genet*. 2013;45(12):1452–8. PMID: 24162737.

- Human Cell Reprogramming for Aging and AD is an initiative supporting the development of induced pluripotent stem (iPS) cells to facilitate the study of the genetic, molecular, and cellular mechanisms underlying human aging and AD.
- The *Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities* conference[402] was held by NINDS in May 2013 in collaboration with NIA and with support from several foundations. The conference included an international group of experts that developed prioritized recommendations for research on AD-related dementias (such as frontotemporal degeneration, Lewy body disease, vascular and mixed dementias), including research relevant to clinical diagnosis and health disparities in AD-related dementias. These recommendations with milestones and success criteria will be formally included in the next revision of the National Plan to Address Alzheimer's Disease.
- NINDS and NIA are supporting a large NIH intramural research project in which researchers will perform whole-exome sequencing of DNA samples from more than 1,500 people with frontotemporal dementia (FTD) and 1,300 people with dementia with Lewy Bodies to characterize chromosomal regions that are associated with a risk of developing these diseases. This project is part of a large international collaboration to understand the genetic causes of these AD-related dementias.
- Research indicates that vascular disease contributes to the development and progression of AD. In a recent study,[403] researchers used transgenic mice to study how beta-amyloid interacts with pericytes, cells that are important for controlling the movement of molecules into and out of blood vessels in the brain. They found that beta-amyloid deposition impairs the function of pericytes, decreasing their ability to remove beta-amyloid from the brain and causing it to accumulate further. These findings suggest that pericytes and other blood-brain barrier cells may be new therapeutic targets for treating AD.

NIH currently supports over 35 clinical trials investigating a wide range of interventions to prevent, slow, or treat AD and/or cognitive decline; many of these trials are coordinated through the long-running AD Cooperative Study. Examples of highly promising studies include a trial on a nasal-spray form of insulin to delay memory loss and preserve cognition and a trial of a monoclonal antibody against beta-amyloid in healthy older people who have brain amyloid deposits and are thus at risk of developing AD. Finally, a joint effort between NIA and the Alzheimer's Association has made possible the first revision of the clinical diagnostic criteria for AD in 27 years. The new guidelines address the use of imaging and biomarkers to determine whether AD causes changes in the brain and body fluids.

PD ranks among the most common late-life neurodegenerative diseases, with a prevalence of 1 percent in individuals over the age of 60. People with PD progressively lose control of purposeful movement and can experience a variety of other symptoms, such as cognitive impairment, mood disorders, sleep disorders, and constipation, which significantly impair their quality of life. Current PD treatments, including dopaminergic drugs and deep brain stimulation via surgically implanted electrodes, may alleviate the movement symptoms of PD, but they also have unwanted side effects and cannot halt the ultimate progression of the disease. Recent studies funded by NIH have highlighted the importance of exercise for maintaining function and reducing disability in people with PD, and NIH continues to fund studies to determine the best exercise programs for people living with PD.

Developing new treatments to cure PD or halt disease progression will require a deeper understanding of the molecular and cellular basis of the disease and new or improved tools and methods to translate those discoveries into treatments. NINDS supports numerous investigator-initiated grants for PD research and funds 10 Morris K. Udall Parkinson's Disease Centers of Excellence across the country. These centers, which were authorized by the Morris K. Udall Parkinson's Disease Research Act of 1997, foster multidisciplinary research using specialized methods relevant to the study of PD. In addition, the Centers for Neurodegeneration Science Program, funded by NIEHS, strengthens the interchange among geneticists, clinicians, epidemiologists, and scientists engaged in PD research on the interaction of environmental risk factors (e.g., agricultural pesticides) with proteins and pathways implicated in genetic forms of PD. One of the biggest obstacles to translating promising laboratory discoveries

[402] http://www.ninds.nih.gov/ADRD2013.
[403] Sagare AP, et al. *Nat Commun*. 2013;4:2932. PMID: 24336108.

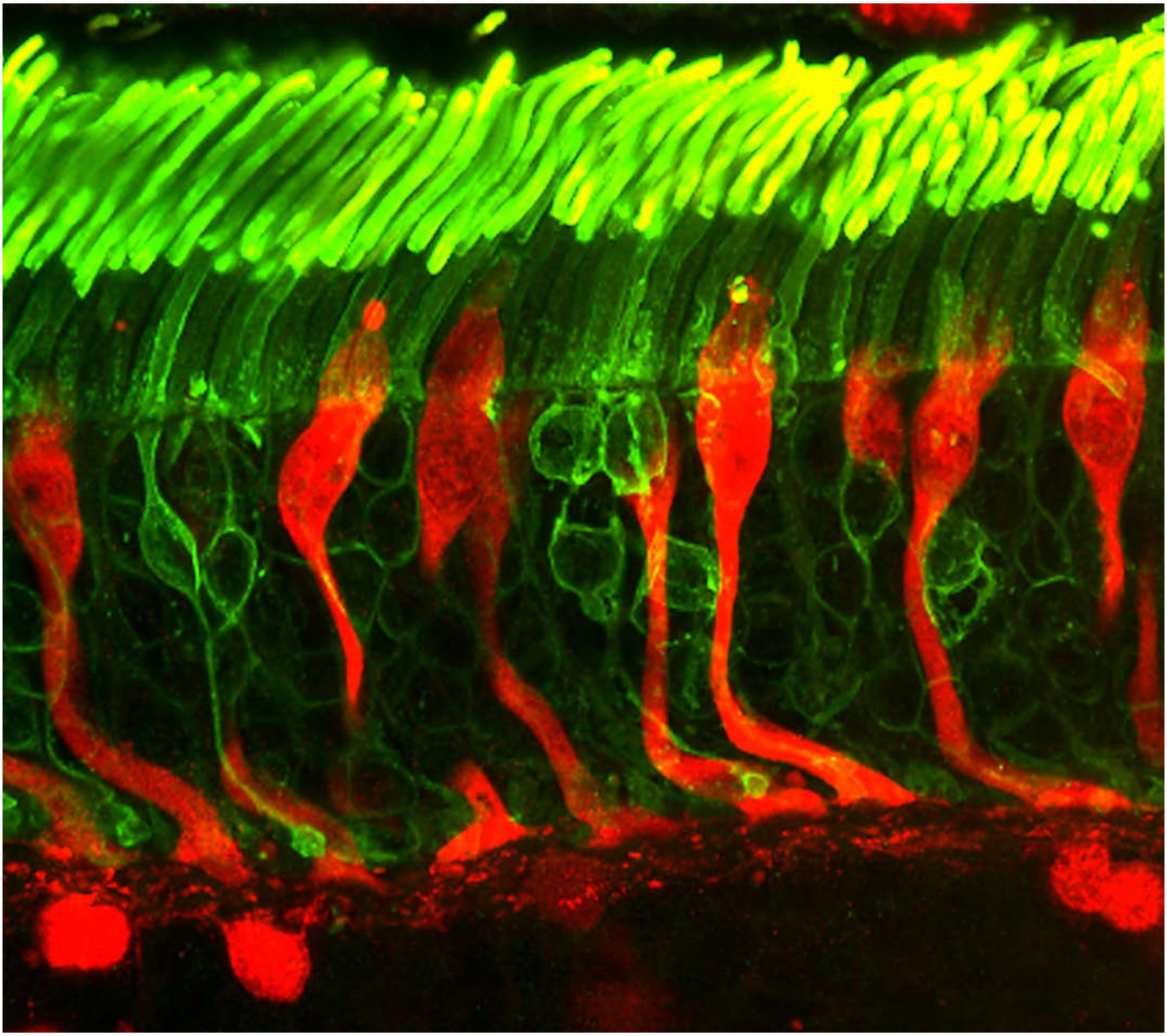


Figure 3-6. *Human retina with rod photoreceptors (green) and cone photoreceptors (skinny red cells in middle) and horizontal cells (round red cells at bottom). Credit: Robert Fariss, Ph.D., NEI.*

into treatments that will cure or slow progression of PD has been the lack of validated biomarkers that can be used to improve diagnosis, track disease progression, and serve as reliable and rapid outcome measures in clinical trials. NINDS supports two biomarkers programs, the NINDS Parkinson's Disease Biomarkers Program and BioFIND, which seek to identify PD biomarkers as well as promote standardization of protocols and broad sharing of biospecimens and data.

Researchers studying neurodegenerative diseases are making use of iPS cells derived from skin cells of affected patients to gain insights into disease mechanisms and facilitate drug discovery. For example, NINDS-supported researchers have used patient-derived iPS cells to understand how neuronal degeneration results from a mutation in a gene known as *C9orf72* that is linked to familial forms of FTD and ALS.[404, 405] This research

[404] Donnelly CJ, et al. *Neuron*. 2013;80(2):415–28. PMID: 24139042.
[405] Haeusler AR, et al. *Nature*. 2014;507(7491):195–200. PMID: 2459854.

demonstrates the power of iPS cells and identifies a potential molecular target for new therapies. NINDS also has supported iPS cell consortia, which have developed iPS cells from people with PD, Huntington's disease, ALS, and FTD. Cell lines developed by the consortia are widely available through the NINDS Human Genetics Repository at the Coriell Institute for Medical Research and are being used by academic and industry researchers around the world.

Many of the leading causes of blindness are due to neurodegenerative diseases. In the retina, genetic mutations in key proteins cause light-sensitive photoreceptor cells to degenerate and die. In a landmark clinical trial, NEI researchers used gene transfer to restore functional vision to children and young adults with Leber congenital amaurosis, a severe retinal degenerative disease caused when a person inherits two mutant copies of the *RPE65* gene. Since publication of these preliminary findings in 2008, NEI investigators found evidence that despite adding a functional copy of *RPE65* to restore function, retinal degeneration continues in patients, ultimately counteracting the benefits of the therapy.[406]

Stargardt disease and age-related macular degeneration (AMD) are neurodegenerative diseases in which atrophy of the retinal pigment epithelium (RPE), a tissue that supports and nourishes photoreceptors, ultimately causes these neurons to die as well. NEI investigators are developing RPE derived from iPS cells to replace diseased cells and prevent vision loss for millions of Americans.[407] Although many neurodegenerative diseases may be caused by rare mutations, NEI is funding research on more general therapy options using neurotrophins, factors that protect neurons from degeneration.[408]

Moreover, neurons are not unique in their vulnerability to progressive or degenerative diseases. Muscular dystrophies (MD) are a class of neuromuscular disorders that lead to progressive muscle weakness and degeneration. NIH support for research on MD includes funding for the congressionally-mandated Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers[409] (also see the information on Wellstone MD Cooperative Research Centers in Chapter 4), in addition to a wider portfolio including basic mechanistic studies, preclinical therapy development, and clinical investigations of many forms of MD. Progress in therapy development for MD has been promising. For example, an NIH-supported research team is developing a treatment for Duchenne muscular dystrophy (DMD) based on a protein called biglycan, part of a specialized structure on the surface of muscle cells that is important for muscle fiber stability and function. The researchers have developed biglycan into a form that can be tested as a therapy for DMD and are moving toward clinical trials in patients. NIH also has supported the development of genetic modification therapies using antisense oligonucleotides, which are short segments of DNA or RNA engineered to bind and inactivate, or skip, the mutated region of a gene, allowing the gene to produce a functional protein. NIH-funded research has fostered a public-private partnership to test an antisense oligonucleotide therapy in animal models of myotonic dystrophy, and plans for a Phase I clinical trial in patients is underway. Other potential DMD therapies developed with NIH support are also moving toward clinical trial readiness, including gene therapy protocols, antisense oligonucleotide therapy, and NF-Kappa-B inhibitor therapy. A clinical trial of gene therapy for limb-girdle muscular dystrophy type 2D is expected to enroll its first patients in the fall of 2014.

For clinical trials in MD to succeed, researchers need biomarkers that can be measured to assess disease progression and response to interventions. As part of a large natural history study of DMD and other efforts, NIH supports research to identify biomarkers in the blood and to develop and validate noninvasive biomarkers based on MRI and electrical impedance myography.

Multiple sclerosis (MS) is the most common of a number of diseases that lead to the degeneration of myelin, a fatty substance that sheathes many nerve fibers in the brain and the peripheral nervous system, causing a variety of symptoms including impaired mobility, spasticity, chronic pain, and depression. Despite tremendous efforts, the cause(s) of MS are still elusive. NIH-funded research covers a wide range of MS-related topics, including studies on genetic and environmental risk factors; basic research on myelination, demyelination, and neuron degeneration; the

[406] Cideciyan AV, et al. *Proc Natl Acad Sci U S A*. 2013;110(6):E517-25.PMID: 23341635.
[407] Barhti K. *PLoS Genet*. 2012;8(7):e1002757. PMID: 22792072.
[408] Birch DG, et al. *Am J Ophthalmol*. 2013;156(2):283–92. PMID: 23668681.
[409] http://www.wellstonemdcenters.nih.gov/index.htm.

blood-brain-barrier breakdown in MS; the CNS's immune system function; optic neuritis (i.e., visual impairment due to inflammation or demyelination of the optic nerve); mechanisms underlying gender differences in the incidence of MS; and development of better strategies to diagnose MS and monitor disease progression. For example, Phase I/II clinical trials, including studies conducted at NIH CC, are investigating the safety and efficacy of immunotherapies, anti-inflammatory drugs, mesenchymal stem cells, nutritional supplements, and hormonal treatments.

Advancing Neuroscience Research through Collaboration

Federal neuroscience research involves collaboration across NIH, HHS, and several other executive branch departments, including DoD, the VA, and the Department of Education (ED).

On April 2, 2013, President Obama proposed the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative as "the next great American project." The BRAIN Initiative has been described as a bold initiative that can transform not only our fundamental understanding of the brain, but also revolutionize our approach to brain diseases.[410] The BRAIN Initiative is jointly led by NIH, DoD's Defense Advanced Research Projects Agency, and NSF. NIMH and NINDS are the Institute leads for the NIH BRAIN Initiative efforts, and the NIH Director tasked a working group of his Advisory Committee to the Director to identify high-priority areas of research for FY 2014 funding and to develop a long-term scientific plan. In September 2013,[411] based on recommendations from the BRAIN Working Group, the NIH Director approved initial priorities to guide $40 million of NIH FY 2014 funding within the BRAIN Initiative. The working group continued its efforts to develop a longer term scientific plan, which was presented to the Advisory Committee to the Director in June 2014. Private organizations also are committed to ensuring success through investment in the initiative. As a result of this concerted effort, new technologies will be invented that will lead to a better understanding of the brain and may ultimately result in new treatments and even cures for devastating disorders and diseases of the brain and nervous system.

Since its inception in 2004, the NIH Blueprint for Neuroscience Research[412] has been a successful model of trans-NIH collaboration, bringing together 16 NIH ICs and Offices that support neuroscience research. The Blueprint continues to support clinical assessment tools for neurological and behavioral function and for widely used neuroimaging, neuroinformatics, and genetics and animal model resources. The NIH Blueprint also supports training programs for neuroscience researchers, including programs focused on interdisciplinary research training, computational neuroscience, neuroimaging, and translational research. In addition, in 2011, the Blueprint initiated three Grand Challenges projects of larger scope focusing on understanding the connectivity of the human brain, neuropathic pain, and the development of treatments for brain disorders:

- The Human Connectome Project Grand Challenge is an ambitious effort to map the neural pathways that underlie human brain function. This project is leading to major advances in imaging resolution and consequently to a better understanding of the development and structure of the brain. The project has set the stage for future studies of abnormal brain circuits in many neurological and psychiatric disorders. Extensions of the project have been approved to adapt the technology to additional sites and equipment, to look at younger and older ages, and to study groups vulnerable to disease.
- The Blueprint Neurotherapeutics Network Grand Challenge was established to bridge the gap in drug development between academic and industry research. The Network offers neuroscience researchers a "virtual pharma" to develop promising compounds from chemical optimization through Phase I clinical testing. It has succeeded beyond expectation, with (currently) six candidates that may move into Phase I trials. A second phase of the project with additional funding has been approved.
- The Grand Challenge on Pain supports research to understand the changes in the nervous system that lead to the transition from acute to chronic pain that persists beyond the time of healing and is difficult to treat. One goal of the initiative at its outset was to

[410] Insel TI, et al. *Science*. 2013;340(6133):687-8. PMID: 23661744.
[411] http://www.nih.gov/news/health/sep2013/od-16.htm.
[412] http://neuroscienceblueprint.nih.gov/.

enhance collaboration between researchers in the pain field and those with expertise in neuroplasticity. Nine multiyear projects were supported under this initiative with research topics on genetic, molecular, and neural circuitry changes that contribute to the transition from acute to chronic pain states.

Three new NIH Blueprint for Neuroscience Research short-term projects were initiated and completed within the report period:

- Tools to Enhance Studies of Glial Development, Aging, Disease, and Repair is a program that facilitates research into glial neurobiology. Glial cells recently have been found to have neuron-like functions leading to an increase in glia research activity. This initiative supported the development of new (or modified) tools that have the potential to enhance the pace of research into the roles of glial cells during neurodevelopment, disease, and plasticity.
- The Cre Driver Mouse Characterization project follows a previous Blueprint Project supporting the development, generation, and initial characterization of more than 100 mouse lines that can be used to enable more anatomically precise neuroscience research. The current project generated additional data on a subset of these lines.
- "OMICS" Tool Development is a program that develops tools to look comprehensively at genes and proteins active at the synapse and gather basic information, such as how many and which genes or proteins are active in a given location in the brain at a given time. These technologies can potentially advance broad areas of neuroscience, such as disease research and therapeutic target discovery.

Support also has continued into or throughout this period for the following previously initiated NIH Blueprint for Neuroscience Research initiatives: K-12 Science Education, the Neuroscience Information Framework, and the Neuroimaging Informatics Tools and Resources Clearinghouse. (For more information on these initiatives, see the FY 2010-2011 Biennial Report.)

Many other examples of collaborative activities in neuroscience research exist beyond the Blueprint. For example, on the NIH campus, the nearly completed 500,000-square-foot John Edward Porter Neuroscience Research Center will foster collaboration by providing laboratory space for more than 800 cross-disciplinary researchers for nine ICs, generating discoveries in structural biology, synaptic processing, sensory systems, neurodevelopment, neurodegeneration, behavior, genetics, and high-resolution microscopy.

To help investigators share data from clinical studies on neurological disorders, NINDS initiated an effort called Common Data Elements.[413] NINDS has worked with disease-specific experts and other stakeholders as part of this program to develop standards to facilitate data collection, analysis, and sharing across the research community. To date, this effort has led to the development of a set of core and disease-specific data elements for headache, spinal cord injury, stroke, epilepsy, PD, ALS, Huntington's disease, Friedrich's ataxia, MS, TBI, and four neuromuscular diseases (spinal muscular atrophy, congenital muscular dystrophy, Duchenne muscular dystrophy, and myasthenia gravis).

The TBI Common Data Elements Program provided an essential foundation for the joint NIH–DoD development of the Federal Interagency Traumatic Brain Injury Research (FITBIR) database. FITBIR allows qualified researchers to share and compare data across studies. Together, Common Data Elements and FITBIR make possible a major new initiative, the International Initiative for TBI Research, a collaboration among NIH, DoD, the European Commons Research Directorate, and the Canadian Institutes of Health Research to advance clinical TBI research, treatment, and care. This major multisite prospective observational study will include 3,000 adults and children with TBI in the U.S. and 11,000 patients in total. Complementing this international effort, another multicenter U.S. study of 1,000 children is evaluating the effectiveness of six major critical care guidelines for severe, pediatric TBI that are currently based on expert opinion, rather than compelling experimental evidence.

[413] http://www.commondataelements.ninds.nih.gov/#page=Default.

Figure 3-7. *Participants in a yoga class meditating while in the lotus pose. Credit: ©Bob Stockfield, courtesy of NCCAM.*

NIH also collaborates with DoD through the Center for Neuroscience and Regenerative Medicine,[414] which brings together scientists from the NIH intramural program, the Uniformed Services University of the Health Sciences, and the Walter Reed National Military Medical Center to cooperatively conduct preclinical and clinical research in TBI diagnosis and treatment in both civilian and military populations in the National Capital area.

Several NIH ICs lead or participate in interagency coordinating committees and working groups focused on conditions affecting the brain and nervous system. In addition to the IACC, led by the Office of Autism Research Coordination in NIMH, NINDS leads an interagency epilepsy working group, which includes broad representation across NIH, other federal agencies, and the research and patient advocacy communities. The group, known as the Interagency Collaborative to Advance Research in Epilepsy, meets annually to share information on epilepsy research activities, discuss research opportunities, and build collaborations.[415]

Other activities include the Joint NSF/NIH Initiative to Support Collaborative Research in Computational Neuroscience, a collaboration among seven NSF directorates and offices, nine participating NIH ICs, and

[414] http://www.usuhs.mil/cnrm/index.html.

[415] http://www.ninds.nih.gov/research/epilepsyweb/researchers/ICARE/index.htm.

the German Federal Ministry of Education and Research. The program supports innovative, collaborative science and engineering research on brain function, integrating computational models and methods with neuroscience and emphasizing data sharing. In addition, NIH IC directors participate in the Institute of Medicine (IOM) Forum on Neuroscience and Nervous System Disorders, which focuses on building partnerships to further understand the brain and nervous system, disorders in their structure and function, and effective clinical prevention and treatment strategies.

NIMH has partnered with DoD to conduct the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS), the largest study of suicide and mental health among military personnel ever undertaken. The rate of suicide among active duty Army soldiers exceeded the civilian rate from 2009-2012. This initiative seeks to identify risk and protective factors, including neurobiological factors that will help the Army develop effective strategies for reducing rising suicide rates. Moreover, President Obama issued an Executive Order in August 2012 requesting "all hands on deck" to ensure better outcomes for military personnel and their families.[416] A year later, the President announced the National Research Action Plan[417] after months of planning between DoD, VA, NIH, and ED. These departments reviewed the state of the science on PTSD, suicide, and TBI; the current research portfolios; and the opportunities for progress. Together they have committed to transforming the research landscape to accelerate progress.

Military personnel and veterans struggle with tremendous health challenges, including PTSD, TBI, depression, anxiety, sleep disturbances, and substance abuse problems. For many, these conditions are further exacerbated by comorbid pain disorders. NCCAM has begun collaborating with DoD and VA to expand the evidence base for the use of nonpharmacological approaches to manage pain and comorbid symptoms in military and veteran populations. Several research studies suggest that mind-body interventions, such as meditation or mindfulness, yoga, acupuncture, massage, and cognitive-behavioral interventions, may hold promise for managing some of the symptoms experienced by military personnel and veterans, although additional research is warranted. In 2012, NCCAM issued an FOA to encourage collaborative activities to promote research on integrative approaches to symptom management in military populations, and in 2013, NCCAM joined NIDA and NIAAA in an FOA for research on the prevention of alcohol and other drug abuse and associated physical and psychological health problems in military personnel, veterans, and their families.

In the wake of the tragic events that took place in December 2012 in Newtown, Conn., President Obama signed 23 executive orders designed to address the problem of gun violence in America; three of the executive orders specifically focused on mental health and resulted in several mental health initiatives. In collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA), NIMH is participating in the National Dialogue on Mental Health and Project AWARE. Launched on June 3, 2013, the National Dialogue on Mental Health seeks to engage communities in conversation, develop and distribute a discussion guide that contains scientific facts about mental illnesses and substance abuse, and improve the flow of people from referral to treatment.[418] Project AWARE aims to increase mental health literacy in schools and among youth and families, support people in crisis, create clear pathways to care, reduce negative attitudes, and help school districts effectively interact with a variety of local organizations to ensure referral for students with mental health concerns.

The National Action Alliance for Suicide Prevention is a public-private partnership that includes representatives from NIH, CDC, SAMHSA, the U.S. Army, and other federal entities. The Action Alliance's mission is to help guide the implementation of the goals and objectives set forth in the National Strategy for Suicide Prevention (NSSP). The Action Alliance recently released the revised NSSP, which called for a prioritized research agenda. Based on an intensive process of gathering input from many stakeholders and experts, a suicide prevention plan is being developed with a goal of shaping research to more efficiently reduce morbidity (i.e., suicide attempts) and mortality (i.e., deaths from suicide). NIMH is co-chairing the Action Alliance's Research Prioritization Task Force (RPTF), which aims to identify gaps in suicide research, including neuroscience research, that demonstrate promise in advancing the goal

[416] https://www.whitehouse.gov/the-press-office/2012/08/31/executive-order-improving-access-mental-health-services-veterans-service.
[417] http://www.whitehouse.gov/sites/default/files/uploads/nrap_for_eo_on_mental_health_august_2013.pdf.
[418] http://www.mentalhealth.gov/.

of reducing suicide through prevention.[419] In 2013, the RPTF published a paper explaining its strategic public health approach to prioritizing suicide prevention research. The approach, which is organized along three dimensions—accessibility of high-risk subgroups, timeline of opportunity, and level of support for prevention and intervention—will guide funding decisions.[420] The RPTF has also discussed the approach with the research community through conference presentations and an NIH Request for Information.[421]

Research Domain Criteria Project

The Research Domain Criteria (RDoC) project is the implementation of Strategy 1.4 of the 2008 NIMH Strategic Plan: "Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures."[422] The diagnostic categories represented in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* and the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* remain the contemporary consensus standard for how mental disorders are diagnosed and treated, but they are rooted almost entirely in diagnoses based on symptoms, rather than on disease mechanisms. Looking forward, however, NIMH seeks to lay the groundwork for a future diagnostic system that more directly reflects modern brain science. The RDoC effort aims to define basic dimensions of functioning across multiple units of analysis, from genes to neural circuits to behaviors, cutting across disorders as traditionally defined. The intent is to translate rapid progress in basic neurobiological and behavioral research to an improved integrative understanding of psychopathology and the development of new and/or optimally matched treatments for mental disorders. Thus, NIMH has begun encouraging prospective applicants to conceptualize their research questions in terms of RDoC domains and associated constructs in order to explain more fully the complete range of normal to abnormal functioning.[423] The Institute anticipates that this effort will have a profound impact on our understanding of mental illnesses.

[419] http://actionallianceforsuicideprevention.org/task-force/research-prioritization.
[420] http://www.ncbi.nlm.nih.gov/pubmed/23628664.
[421] http://grants.nih.gov/grants/guide/notice-files/NOT-MH-12-017.html.
[422] http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml.
[423] RFAs released in FY 2011-2013: http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-12-100.html; http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-13-080.html; http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-030.html; and http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-050.html.

Life Stages, Human Development, and Rehabilitation

Interactions among biological processes and physical and psychosocial factors in the environment shape an individual's health and functional capacities from the earliest formation of cells, tissues, organs, and organ systems through childhood, adulthood, and old age. Human development progresses most rapidly during gestation and early childhood, but continues throughout the course of life. Each developmental stage lays the foundation for health or illness in subsequent stages.

Understanding precisely what happens during developmental "windows" of heightened sensitivity to infections, toxic exposures, personal behaviors, and a host of other environmental factors is essential to learning how and when to intervene most effectively to prevent or lessen chronic and disabling conditions. This concept, which has been termed the Developmental Origins of Health and Disease (DOHaD), is based on extensive human epidemiologic data and experimental animal models. DOHaD data and models from NIH-supported research demonstrate that the risk of poor adult health is associated with environmental influences during fetal development and infancy, as well as influences affecting transgenerational inheritance. Initial research on DOHaD focused primarily on nutritional factors contributing to disease; however, other environmental factors during development now also are being linked to the risk of noncommunicable diseases such as diabetes, cardiovascular disease (CVD), metabolic syndrome, and chronic lung diseases. The potential implications of DOHaD research are great, as more than 35 million deaths per year—60 percent of all global deaths—are attributed to noncommunicable diseases.[424]

This area of NIH research also encompasses medical rehabilitation, including circuit plasticity and tissue regeneration, to optimize the functioning of individuals with disabling conditions. Medical rehabilitation research is the study of physiologic mechanisms, methods of treatment, and devices that serve to improve, restore, or replace

[424] Alwan A. *WHO Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases*. 2008. Geneva, Switzerland: WHO. Available at: http://www.who.int/nmh/Actionplan-PC-NCD-2008.pdf.

underdeveloped, lost, damaged, or deteriorated function. A key aspect of medical rehabilitation research is its focus on the effects of functional problems on the whole person, rather than a single organ system. Thus, this type of research views the individual in the context of a dynamic system of interacting variables, including biological, psychosocial, and environmental factors.

The role of developmental processes in the risks for common and rare disorders and in rehabilitation science means that the scope of NIH research in life stages, human development, and rehabilitation is quite broad. This research area includes basic research on molecular and cellular processes to gain insights into the trajectories of human development, injury response, disease, and aging as well as to harness developmental processes for therapeutic and rehabilitative uses. This research area also includes the collection and analysis of data over the lifespan or over a specific period of interest, such as childhood or older age. Such studies can suggest the relative contributions to health or to specific disorders of environmental exposures and ongoing developmental and disease processes. Also included are studies of specific disorders, with an emphasis on an individual's life stage or developmental status.

Research in life stages and human development is supported by a number of ICs. NICHD, the Institute with statutory responsibility for child health and human development research, conducts and supports research programs in reproductive health and in the developmental processes that begin before conception and continue through adolescence. NIA conducts and supports research on both the maintenance and loss of functions during the aging process, diseases associated with aging, and the problems and needs of older individuals and their caregivers. NINR supports research across all life stages to build the scientific foundation for clinical practice and for managing and eliminating symptoms caused by illness; NINR also is the designated lead Institute for end-of-life research.

Studies of the developmental origins of health and disease suggest that exposures occurring while tissues and organs are developing increase risk for disease in all stages of life and sometimes in future generations. Diseases and conditions such as obesity, type 2 diabetes, insulin resistance, asthma, CVDs, dyslipidemia, cognitive and behavioral disorders, neurodegenerative diseases, some cancers, and reproductive disorders are thought to result at least in part from environmental exposures that occur in the womb or during childhood. Researchers supported by NIEHS are working to increase the knowledge of how certain diseases or conditions originate during critical windows of development.

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

Many sections of this report include data on the burden of illness of specific conditions in which developmental-environmental interactions are or may be implicated. Comprehensive data on the total burden of these conditions do not appear to be available. The magnitude of this burden, however, is exemplified by just a single condition, the complex problem of obesity and its associated conditions, including type 2 diabetes, CVD and stroke, pregnancy complications, certain cancers, osteoarthritis, liver and gall bladder disease, and depression. CDC estimates the prevalence of obesity among adults in the U.S. aged 20 and older as 34.9 percent and the prevalence of obesity in children and youth aged 2–19 as 16.9 percent.[425] Overweight and obesity also exert a substantial economic toll on the U.S., with the medical spending attributable to obesity estimated to be $147 billion for the year 2008.[426]

Estimating the burden of functional limitations for which rehabilitation may be indicated is complicated by lack of consensus on the definition of "disability," appropriate survey measures, and other issues. The IOM defines disability as impairments in body structure or function,

[425] Ogden CL, et al. *JAMA*. 2014;311(8):806–14. PMID: 24570244.
[426] Finkelstein FA, et al. *Health Affairs*. 2009;28(5):w822–31. PMID: 19635784.

limitations on activities such as dressing and other daily personal care, and limitations on participation in such activities as school and work. IOM reported that 40 million–50 million individuals,[427] or about one in seven Americans, have some type of disability.

NIH Funding for Life Stages, Human Development, and Rehabilitation Research

NIH funding for rehabilitation research was $449 million in FY 2012 and $446 million in FY 2013.[428] Currently, NIH does not collect the trans-NIH funding data necessary to provide an aggregate figure for expenditures on life stages and human development research.

Summary of NIH Activities

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

[427] http://www.nap.edu/openbook.php?record_id=11898&page=1.
[428] http://report.nih.gov/categorical_spending.aspx.

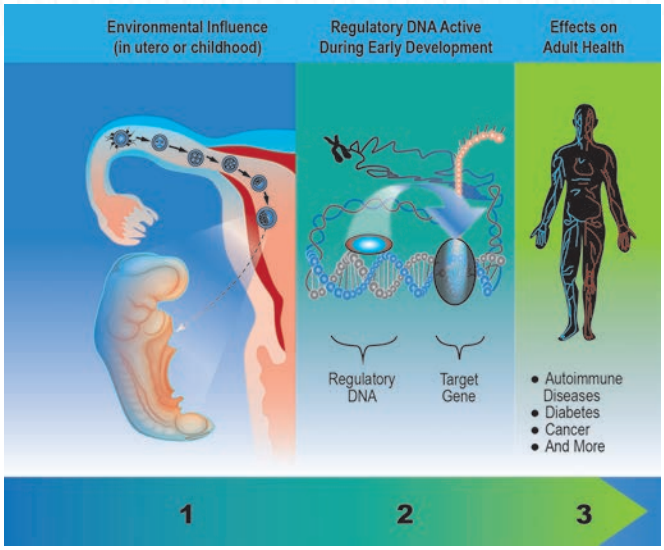


Figure 3-8. *Early environmental influences (1) can impact regions of regulatory DNA active in early development. (2) Epigenomics researchers found that many genetic variants linked to adult-onset disease (3) are located in these regions, potentially linking early environmental influences with development of adult diseases. Credit: A Decade of Discovery—The NIH Roadmap and Common Fund.*

Human Development

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

It is now known that epigenetic influences on the expression of genes may be critical mechanisms for gene-environment interactions that influence health and human development. Understanding these subtle interactions is an essential step toward discovering treatments and preventive strategies. NIH has established the Common Fund Epigenomics Program[429] to stimulate the creation of important new scientific resources for epigenetics researchers and thus speed progress toward applications that affect human health and common, complex human diseases. A major effort in the program is characterizing the epigenome; that is, creating a catalog of stable epigenetic modifications that occur in the genome (all genes encoded in the DNA). The Epigenomics Program has produced almost 90 reference maps of epigenomic modifications in healthy human cells

[429] https://commonfund.nih.gov/epigenomics/index.

and tissues. Additionally, researchers in the program have published landmark studies on the role of epigenomic modifications in normal development and disease. Researchers have also identified genetic variants linked to adult-onset diseases that lie in regions of DNA regulating genes during the early stages of development, providing a potential mechanism to explain the observation that some environmental exposures in utero or during early childhood are known to increase risk of diseases that produce symptoms years or even decades later.

NIH investments in understanding and developing interventions for Fragile X and Down syndrome and other intellectual and developmental disabilities include support for 14 centers focusing on these types of disabilities. These centers provide core research resources, such as genetics and proteomics services, as well as clinical infrastructure, such as neurobehavioral testing, for a wide range of studies. Multiple NIH-supported programs focus on ASD. For example, the Autism Centers for Excellence include six centers (focusing research on possible causes of ASD, including genetic, immunological, and environmental factors) and five networks (focusing on causes, preventive interventions, and improved treatment). More information on neurodevelopmental disorders, such as Down syndrome and autism, can be found in the "Neuroscience" section of this chapter.

Pediatric disorders of vision can often be treated if diagnosed in time. Retinopathy of prematurity (ROP) is abnormal blood vessel development in the eyes of some infants born severely premature. ROP can lead to blindness if not treated in time. In 2012 and 2013, NEI funded a clinical trial that used telemedicine as a tool for doctors to diagnose ROP remotely in premature infants born in rural and underserved areas. Similarly, amblyopia (sometimes called "lazy eye") is reversible through eye patching of the dominant eye if diagnosed early. However, some patients do not respond to the standard eye patching protocol of two hours per day. A recent NEI clinical trial found that patching six hours per day was effective in treating persistent amblyopia.[430]

[430] Pediatric Eye Disease Investigator Group. *Ophthalmology*. 2013;120(11):2270–7 PMID: 23755872.

Life Stages

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

For example, the NIH-supported Breast Cancer and the Environment Research Program (BCERP) is a transdisciplinary initiative cosponsored by NCI and NIEHS in which basic scientists, epidemiologists, clinicians, and community partners work together to examine the effects of environmental exposures that may predispose a woman to breast cancer throughout her life. BCERP Windows of Susceptibility Studies are examining how breast cancer risk relates to environmental exposures that occur during susceptible times in development, and the BCERP Puberty Study is following more than 1,200 young girls to understand better the predictors of early puberty, which is associated with increased breast cancer risk.

The tendencies toward risky behaviors attributed to immaturity of the brain in adolescence makes this developmental stage of interest in studies of substance abuse and addiction. In seeking to understand how developmental stage may influence vulnerability to or protection from drug abuse, scientists are beginning to understand how a range of environmental variables, including quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics, influence brain development and behavior. Better understanding of relationships between developmental stages and disease processes may be critical to the efficacy of therapeutic interventions.

On the other end of the age spectrum, NIH conducts and supports a large and diverse research portfolio on aging and age-related diseases, including biochemical, genetic, and physiological mechanisms of aging in humans

and animal models; structure and function of the aging nervous system; social and behavioral aspects of aging processes; and pathophysiology, diagnosis, treatment, and prevention of age-related diseases and disabilities. One of the longest ongoing longitudinal studies of aging ever conducted, the Baltimore Longitudinal Study of Aging (BLSA) has been active for more than half a century. The underlying goal is to distinguish changes due to "normal aging" from those generated by age-associated conditions. Findings from the BLSA in this regard have contributed substantially to current knowledge of the physiology of aging. Incorporating major technological advancements in the assessment of physiologic and biomarkers of aging and theoretical refinements, the BLSA continues to pursue the following objectives: (1) describe longitudinal physical and cognitive changes that define aging; (2) identify genetic, physical, behavioral, and environmental factors that affect the rate of change in these traits; and (3) understand the interrelationship between aging and chronic disease and other conditions as well as their independent and joint impact on age-related decline.

To develop a comprehensive picture of the health, well-being, and disability of older Americans, NIH supports the Health and Retirement Study (HRS), the National Health and Aging Trends Study (NHATS), and the Mid-Life in the U.S. (MIDUS) project. The HRS has surveyed approximately 20,000 Americans aged 50 and older every two years since 1992, collecting data on income, work, assets, pension plans, health insurance, disability, physical health and functioning, cognitive functioning, psychosocial stress, family structure, and health expenditures. Self-report and biomarker measures of health are combined with Medicare data on health services use. The NHATS is the successor to the National Long Term Care Survey and is the source of annual research data on national disability trends and dynamics among the U.S. senior population and on the consequences of late-life disability for individuals, families, and society. The MIDUS project enables the study, over the full life course, of adult behavior, cognitive and emotional function, social conditions, and the emergence of physiological dysregulation and health disparities before the typical ages for onset of disability and diagnosis of major chronic diseases. Data from the first two rounds of collection are available to qualified researchers, and a third wave of data collection began in 2013.

NIA leads most aging research at NIH, including the Interventions Testing Program (ITP), which supports the testing of certain interventions, including foods, diets, drugs, and hormones, with the potential to extend the lifespan and delay disease and dysfunction in a mouse model of aging. ITP investigators found that the drug rapamycin can increase the lifespan in both male and female mice. They subsequently found that acarbose, another drug commonly used to treat type 2 diabetes, increased the median lifespan of male mice by 22 percent. In the same paper, the investigators reported the effects of three other agents on mice lifespan. Two of the agents increased male median lifespan by 8–12 percent, but had no effect on female lifespan, while the third agent had no effect on male lifespan and only a minor increase in maximum female lifespan.[431]

In 2012, NIA established a similar program to identify pharmacological interventions that increase lifespan and/or health span when tested using multiple species of a simple invertebrate nematode (e.g., *Caenorhabditis elegans*). Human populations are genetically diverse, and any intervention that extends lifespan/health span needs to do so within a variety of genetic backgrounds. Testing of promising compounds in a variety of genetic backgrounds within a species with a short, well-studied lifespan and health span should accelerate the current rate of discovery.

Research on aging and age-related disorders is conducted in other ICs as well. For example, NIDCD-funded investigators hope to identify gene mutations that contribute to age-related hearing loss, understand structural consequences of such mutations, and investigate protein function of these genes to inform better prevention and treatment strategies. A new initiative exemplifying the collaborative and interdisciplinary nature of research on aging is the NIH GeroScience Interest Group (GSIG).[432] This trans-NIH committee was established in 2012 to accelerate and coordinate efforts to promote further discoveries on the common risks and mechanisms behind age-related diseases and conditions by developing a collaborative framework that includes multiple NIH Institutes. By pooling resources and expertise, the GSIG identifies

[431] Harrison DE, et al. *Aging Cell*. 2014;13(2):273–82. PMID: 24245565.
[432] http://sigs.nih.gov/geroscience/Pages/default.aspx.

major cross-cutting areas of research and proposes coordinated approaches to identify hurdles and envision solutions. In 2013, the GSIG and several private-sector partners convened a national Summit titled "Advances in Geroscience: Impact on Healthspan and Chronic Disease."

At all stages of life, individuals with chronic or critical illnesses and their families and clinical caretakers need evidence-based guidance and support in managing chronic illness and transitioning to the end of life. End-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on such issues as alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-, and disease-specific factors that make each person's experience at the end of life unique. NIH-supported Centers in Self-Management or End-of-Life research are important loci for interdisciplinary research in this area.

In July 2013, NINR published *Building Momentum: The Science of End-of-Life and Palliative Care. A Review of Research Trends and Funding, 1997–2010*. This report looks at the trends in end-of-life and palliative care (EOL PC) research publications over the past 14 years, including information on federal research awards, funding patterns, and the contributions of public and private investments in EOL PC science.[433] The report addresses the 1997 IOM recommendations for the scientific community to strengthen the research landscape, foster new evidence, and define and implement priorities for increasing the knowledge base for EOL PC. The key findings of the report not only summarize the state of EOL PC research, but also identify gaps that future research efforts could address.

Rehabilitation

The goal of rehabilitation science is to enable individuals with functional impairments associated with congenital disorders, chronic diseases, or such events as stroke or traumatic injury to live full and productive lives as independently as possible. Developmental stages are a central consideration in this research, because differences among age groups, including physiology and physical size,

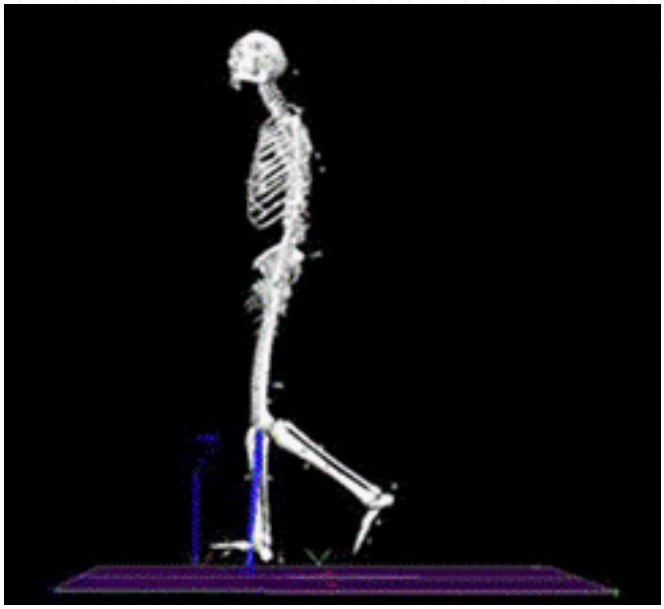


Figure 3-9. *A computer-animated skeleton produced by researchers at the CC Rehabilitation Medicine Department's Functional & Applied Biomechanics Lab. Although the bones were generated by computer, the data used to animate them was precisely recorded from a real patient using a motion-capture system. Credit: CC Rehabilitation Medicine Department.*

psychosocial trajectories, and expected lifespan, must all be taken into account in rehabilitation interventions.

Basic cellular and molecular processes and activity-generated plasticity offer great potential to restore function or support adaptive strategies. Research is being conducted into the pathophysiological mechanisms and tissue responses that underlie functional impairments. Scientists also are seeking to understand the therapeutic potential of different interventions, including molecular and cellular therapies, extrinsic pharmacological and bioengineering supports, and therapeutic exercise, to promote such developmental processes and enhance recovery.

The NIH CC Rehabilitation Medicine Department's Functional & Applied Biomechanics Lab conducts innovative research, including neuromotor assessment and recovery, virtual functional anatomy, and rehabilitation robotics. Beyond movement analysis using infrared cameras or MRI, the lab has expanded its expertise to areas that include state-of-the-science balance assessment, a robotics laboratory, and ultrasound.

[433] http://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/NINR-Building-Momentum-508.pdf.

A focal point for this research is NICHD's National Center on Medical Rehabilitation Research,[434] which emphasizes the rehabilitation and lifelong care of people with physical disabilities resulting from developmental disorders, injury (e.g., stroke, spinal cord injury), musculoskeletal disorders, and aging and degenerative conditions. Following the 2012 publication of the report of the Blue Ribbon Panel on Medical Rehabilitation Research at NIH, the Center began strategizing with other ICs about how to leverage NIH investments in this area of research with enhanced coordination within NIH and with other federal agencies and private-sector organizations.

One avenue of research is the use of stem cells to regenerate tissue. NIDCR-supported scientists have identified unique markers on skeletal progenitor cells from mouse bone marrow, which allows these relatively rare cells to be targeted to increase their numbers. This enrichment can significantly enhance the cells' potential to regenerate bone and cartilage.[435] NIDCR-funded investigators also have shown that modifying proteins that help organize the DNA structure in human bone marrow mesenchymal stem cells (BMMSCs) can change the cell type that is ultimately generated.[436] Ongoing research is now investigating how to translate this knowledge into strategies to influence BMMSC cell fate choices in the bone marrow to promote bone regeneration.

In addition, NIDCR-supported stem cell research may one day allow tooth regeneration. Using a mouse model, NIDCR-funded scientists have made a significant advance by discovering how tooth stem cell populations are maintained during tooth development and maturation, providing critical information toward cell therapy to regenerate teeth.[437] In a recently completed study to define oral wound healing, in comparison to wound healing of the skin, researchers have begun to identify the specific factors that enable rapid and nearly scar-free healing of oral mucosa.[438] These factors not only could improve scar-free healing of a variety of tissues, but also could lead to improved tissue regeneration strategies.

NHLBI is also investing in regenerative medicine research to enhance the capacity of the heart and lungs to repair themselves. For example, 2012 Nobel Laureate Shinya Yamanaka is part of a large inter-institutional team of NHLBI-funded investigators studying how to use a child's own cells to repair a congenital defect or create a tissue graft that could grow as the child ages. Similarly, a recent study showed an exciting possibility for treating lung disease—engineering lung tissue in a dish that could be used for tissue repair and cell therapy. Investigators were able to use stem cells to repopulate rat and human lung scaffolding in cell culture so that it had the markers of lung tissue.[439]

An important focus of rehabilitation research is the intersection among medicine, assistive engineering, and behavioral and psychosocial reports. Scientists explore innovative biomedical technologies and test their capacity to resolve stubborn medical problems and enhance mobility, sensory, cognitive, and other functions of individuals with disabling conditions. NIH projects in rehabilitation also pursue the development of prosthetics, wheelchairs, and other devices to restore or enhance the capacity to function in those who lose limbs because of injury, combat, or complications from diseases such as diabetes.

In one NIBIB-funded project, underway since 2011, researchers are capitalizing on new advances in technology that have resulted in a successful prototype "bionic arm" to create a next-generation "bionic hand." For years, prosthetic hands have consisted of a claw limited to an open and close motion. Researchers aim to demonstrate individual finger control of a prosthetic hand in amputees through implanted sensors. The results thus far are promising, indicating potential for the control of individual fingers.[440]

Also using implantable technology, functional electrical stimulation devices consist of a networked system of small modules and a power source. Some modules stimulate nerves or paralyzed muscles, and others receive and transmit signals from nerves and muscles. The networked system can be customized to restore a broad range of functions, including hand grasp, upper limb movement, abdominal control for maintaining posture, and standing

[434] https://www.nichd.nih.gov/about/org/ncmrr/Pages/overview.aspx.
[435] Chan CK, et al. *Proc Natl Acad Sci U S A*. 2013;110(31):12643–8. PMID: 23858471.
[436] Ye L, et al. *Cell Stem Cell*. 2012;11:50–61. PMID: 22770241.
[437] O'Connell DJ, et al. *Sci Signal*. 2012;5(206):ra4. PMID: 22234613.
[438] http://clinicaltrials.gov/ct2/show/NCT01078467?term=gutkind&rank=3.
[439] Ghaedi M, et al. *J Clin Invest*. 2013;123(11):4950–4962. PMID: 24135142.
[440] Birdwell JA, et al. *J Neurophysiol*. 2013 Sep;110(6):1385–92. PMID: 23803329.

balance and stability to enable patients to transfer themselves from a wheelchair to a bed, giving paralyzed people greater independence.

For people who are paralyzed and confined to a wheelchair, quality-of-life issues such as regaining bladder and bowel control, sexual function, and body temperature regulation may be more important than walking again. These functions restrict independence and mobility more than the use of a wheelchair. Epidural spinal stimulation is showing promise in treating people with severe spinal cord injury and restoring these functions as well as regaining some movement. Patients paralyzed below the chest were able to voluntarily move their toes, ankles, and legs and stand independently while their spinal cords were being electrically stimulated.[441] Researchers are currently working to develop a new high-density stimulator to provide finer, more robust control of locomotion.

Helping patients adapt to using new interventions also is part of NIH's rehabilitation research portfolio. For example, NIDCD-supported scientists are examining the scientific bases of aural rehabilitation and improving the provision of aural rehabilitation services to individuals with hearing loss. Aural rehabilitation refers to enhancing one's perception of spoken communication, particularly through the auditory channel. The rehabilitation includes counseling individuals with hearing loss about the nature and effects of their hearing loss and on intervention options available for them as well as training on how to use these interventions. Such interventions include hearing aids, cochlear implants, other augmentative and alternative communication devices (such as those that integrate communication information from vision and touch), and auditory training programs. NIDCD-supported scientists also are developing more effective interventions for the speech, voice, and language impairments often associated with stroke, cerebral palsy, autism, AD, and other neurologic/neurodevelopmental disorders.

NIDCD-supported researchers are seeking to understand how normal hearing abilities might be preserved and combined with the artificial hearing provided by a cochlear implant. One of the newest cochlear implant designs includes changes in the electrode array so that users with hearing at low frequencies can still use that information in combination with signals from the cochlear implant. The goal is to allow individuals with low-frequency hearing in both ears to receive a cochlear implant with significantly shorter electrode array in one ear. This strategy might provide superior benefits to patients than a conventional cochlear implant in one ear and a conventional hearing aid in the other.

NIDCD-supported scientists are also studying large groups of children who were identified early with hearing loss and received a cochlear implant. Knowledge from this research will shed light on the variables most related to improved speech and language acquisition, as well as reading and higher academic performance, in children with cochlear implants.

In addition, NIDCD supports clinical trials on hearing aids and cochlear implants. One trial is investigating the efficacy of telemedicine versus traditional face-to-face post-implant for aural rehabilitation in children after cochlear implantation. Another randomized trial is collecting data to help health care providers determine which method of intervention—a hearing aid or a cochlear implant—is most beneficial for speech and language development in children with developmental delay. Two additional trials are working to help improve the satisfaction of hearing aid users by testing different ways to improve how well a hearing aid user can detect and interpret spoken sounds in a noisy environment.

[441] Angeli CA, et al. *Brain*. 2014;137(5):1394–409. PMID: 24713270.

Chronic Diseases and Organ Systems

Chronic diseases are defined by HHS as conditions that last one year or more and require ongoing medical attention and/or limit activities of daily living. Chronic diseases place a considerable burden on the U.S. health care system, the national economy, and the health and lives of individual patients and their families. Not all chronic diseases are fatal; however, 70 percent of the 1.7 million Americans who die each year succumb to a chronic disease.[442]

Health-damaging behaviors, such as drug use (e.g., tobacco, excessive alcohol, or other drugs), low levels of physical activity, prolonged time spent in sedentary behavior (which may impair health despite engaging in physical activity at other times), and poor eating habits, contribute to many chronic diseases. Other chronic diseases result from the long-term effects of early exposure to toxins or other environmental factors, especially in individuals with a higher genetic risk of disease. Less common are chronic diseases that may manifest from birth as a result of one or more faulty genes (e.g., sickle cell anemia, hemophilia) or at other times during childhood (e.g., allergies and asthma). Many chronic diseases that lead to significant disability develop over time and become more prevalent with age (e.g., osteoarthritis, chronic kidney disease [CKD], vision loss, hearing loss). Among the U.S. population, some chronic diseases are common, such as heart disease, which is the leading cause of death in the U.S.,[443] whereas other chronic diseases are relatively rare, such as cystic fibrosis (CF), which affects approximately 30,000 Americans. Certain chronic diseases and conditions represent growing public health issues, such as the increases in obesity and type 2 diabetes in children and adults.

The prevalence and burden of chronic diseases are substantial. About 133 million Americans—nearly half of all adults—live with at least one chronic illness.[444] Chronic disease disables or limits activity for more than 12 percent of all Americans, including about 24 percent of adults 65–74 and 42 percent of adults age 75 and older.[445] The number of adults 50–64 with disability related to a chronic condition, while still small, increased significantly from 1997 to 2007.[446] Notably, the percentage of U.S. children and adolescents with a chronic health condition has increased significantly, from 1.8 percent in the 1960s to more than 7 percent in 2004. Furthermore, the increasing prevalence of patients with one or more chronic disease has a significant impact on health care delivery and the economy; more than 75 percent of health care costs are related to treatment of chronic conditions.[447]

Many chronic diseases and conditions that are common in the U.S., such as type 2 diabetes, obesity, and heart disease, also have a substantial impact on global morbidity and mortality. By 2030, we anticipate that chronic diseases will account for 50 percent of the disease burden in low-income countries and more than 75 percent in middle-income countries. Chronic diseases and conditions already account for over 85 percent of the disease burden in high-income nations.[448]

Many chronic diseases and conditions may affect more than one organ. For example, diabetes can affect the pancreas, heart, kidneys, eyes, and nerve endings in the limbs. People with serious mental illness are more likely to suffer with chronic diseases that are associated with addiction (especially nicotine), obesity (sometimes associated with antipsychotic medication), and poverty (which is associated with poor nutrition and health care), and they may suffer these adverse health consequences at an earlier age than other people. For these reasons, modern medicine requires an integrated understanding of the complex interactions among multiple organs and the nervous, circulatory, immune, and endocrine systems.

Thus, research to combat chronic illness involves significant trans-NIH collaboration in addition to the mission-specific work of each IC. NIH supports (1) basic research on both

[442] CDC. Chronic Diseases: The Power to Prevent, the Call to Control. Atlanta, GA: 2009. Available at http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm.
[443] http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.
[444] CDC. The Power of Prevention: Chronic disease…the public health challenge of the 21st century. Atlanta GA: 2009. Available at: http://www.cdc.gov/chronicdisease/pdf/2009-Power-of-Prevention.pdf.
[445] Adams PF, Kirzinger WK, Martinez ME. Summary Health Statistics for the U.S. Population: National Health Interview Survey, 2012. National Center for Health Statistics. Vital Health Stat 10(259). 2013. Available at: http://www.cdc.gov/nchs/data/series/sr_10/sr10_259.pdf.
[446] Martin LG, et al. *Health Aff (Millwood)*. 2010;29(4):725–31. PMID: 20368601.
[447] CDC. Chronic Diseases: The Power to Prevent, the Call to Control. Atlanta, GA, 2009. Available at: http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm.
[448] Quam L, et al. *Lancet*. 2006;368(9543):1221–3. PMID: 17027712.

normal and disease states of organ systems to understand the initiation and progression of chronic diseases and (2) translational and clinical research on new biomedical and behavioral strategies to prevent, preempt, diagnose, treat, and cure these diseases. The ultimate goal is to reduce or eliminate morbidity and mortality while improving quality of life for those living with these often debilitating conditions.

This section provides information about NIH's activities related to a number of major chronic diseases as well as research on aspects of the function of various organ systems. Additional major chronic diseases are discussed in the sections "Cancer" (cancers of all organs and tissues, including blood), "Neuroscience" (e.g., PD, AD, autism, epilepsy), "Autoimmune Diseases" (e.g., lupus, multiple sclerosis, rheumatoid arthritis [RA], inflammatory bowel diseases [IBDs]), and "Infectious Diseases and Biodefense" (e.g., HIV/AIDS, viral hepatitis). Because some people with certain chronic diseases require transplantation to replace a diseased organ or tissue, this section also highlights organ transplantation research and the related issue of establishing immune tolerance to transplanted organs (i.e., ensuring the organ is not rejected by the recipient's immune system). Research on complementary and integrative health approaches to combating chronic disease also is discussed. NIH supports research to reduce the pain associated with long-term diseases and to find innovative and effective forms of palliative care to relieve disease symptoms. Some of these efforts are highlighted in the "Neuroscience" section.

NIH Funding for Chronic Diseases and Organ Systems Research

Currently, NIH does not collect the data necessary to provide an aggregate figure for expenditures on chronic diseases and organ systems research. Appendix I provides funding estimates for many of the areas of research associated with chronic diseases and organ systems. Because of overlap among the areas of research listed in the table, and because research on chronic disease and organ systems may account for only a portion of the funding for a given area, the figures in Appendix I cannot be used to provide an aggregate number.

Summary of NIH Activities

NIH invests significant resources into the study of chronic diseases, and nearly all NIH ICs support research to understand the molecular and cellular mechanisms of human physiology in the health and disease of organ systems. Such research has the potential to lead to new insights and treatments for chronic diseases, as highlighted in the following subsections. The diverse NIH research portfolio broadly encompasses research on the normal physiology of all organ systems in the body; studies of rare and common diseases in both children and adults; development of devices and technologies for disease detection and diagnosis; evaluation of strategies for prevention and treatment that might be based on pharmaceuticals, behavioral modification, surgical techniques, mechanical devices, or other approaches; and translation of research results into real-world applications or resources for the benefit of patients who live with chronic diseases every day. This section highlights key examples of challenges, progress, and emerging opportunities in NIH-supported research on chronic diseases and organ health.

Cardiovascular Diseases

CVD is a broad term used to encompass many conditions, including heart diseases such as coronary heart disease, cardiomyopathy, heart failure, heart valve disease, sudden cardiac arrest, and congenital heart defects, as well as cerebrovascular disease (including stroke) and other diseases and conditions of the blood vessels, such as peripheral arterial disease and deep vein thrombosis. Coronary heart disease is the most common type of heart disease and a major cause of death in the U.S. for both men and women, and stroke is the fourth leading cause of death in U.S. adults.

As the lead institute for CVD research, NHLBI studies cover the spectrum of basic investigations, clinical and translational research, and implementation science. Basic research is shedding light on potential avenues that could ultimately prevent and treat disease. For example, researchers recently succeeded in generating mature cardiomyocytes (heart muscle cells) in vitro that are the closest approximation of natural human heart tissue to date.

The ability to engineer heart muscle brings scientists closer to developing cell-based therapies and drug screening for patients with heart disease.[449]

New findings also are promising revolutionary new approaches to CVD diagnosis and treatment. For example, researchers studying the blood of patients with thoracic aortic aneurysms (TAA), enlargement of the upper aorta, found high levels of fibrillin-1, an important structural protein that is associated with acute aortic dissection (i.e., separation of layers of the aortic wall). Previous research determined that mutations in the gene for fibrillin-1 result in Marfan syndrome. This research could lead to the development of a blood test to diagnose and manage TAA, replacing costly imaging tests.[450] In another recent study, scientists injected a synthetic modified molecule that stimulates the growth of new blood vessels into the damaged heart muscle of mice after an experimental heart attack. The results showed that such an injection could enhance heart regeneration, improve heart pumping capacity, and enhance long-term survival.[451]

The clinical research funded by NHLBI ranges from observational studies to randomized clinical trials, comparative effectiveness research, and implementation science. NHLBI clinical trials are designed to answer key questions about therapeutic and preventive strategies for major diseases of the heart and blood vessels. Ongoing clinical trials addressing coronary heart disease examine a number of strategies, including medications, stenting, revascularization, and angiography. For example, the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial is evaluating drug therapy versus the use of catheter-directed electrical impulses to control arrhythmia. To address hypertension, NHLBI is sponsoring a number of trials, including the Systolic Blood Pressure Intervention Trial (SPRINT)[452] to determine whether a lower blood pressure target than current standards will reduce the risk of heart and kidney disease, stroke, and/or age-related decline in cognitive function.

Cardiovascular research supported by the Institute spans the lifetime from childhood through adulthood. The NHLBI Pediatric Cardiac Genomics Consortium is a cooperative investigative group that conducts clinical and translational research on the genetic causes of, and outcomes in individuals with, congenital heart disease. The Pumps for Kids, Infants, and Neonates (PumpKIN) program is testing devices to help children born with congenital heart defects or who develop heart failure. Researchers are also using data from an NHLBI-funded registry to risk stratify children with pediatric cardiomyopathy, an approach that can assist physicians in determining which infants are at the highest risk for poor outcomes and in evaluating which of these infants should be considered for a heart transplant immediately after diagnosis. These findings are expected to enable medical teams, genetic counselors, and family planners to jointly and quickly determine the best treatment. Finally, studies in adults with congenital heart disease are helping shed light on barriers in the transition in treatment from childhood to adulthood.

NHLBI also supports programs and networks focused on cutting-edge technologies that involve collaborative and multidisciplinary approaches to CVD research. The Programs of Excellence in Nanotechnology supports multidisciplinary teams to develop nanotechnology-based tools for the diagnosis and treatment of heart, lung, and blood diseases, and to move the translation of these technologies towards clinical application. The NHLBI Gene Therapy Resource Program facilitates the translation of gene therapy research into clinical interventions via provision of resources in the form of preclinical and clinical-grade vector production, pharmacology/toxicology testing, immunology testing, clinical trials–funding assistance, and regulatory support; and the Cardiovascular Cell Therapy Research Network provides an infrastructure to evaluate innovative cell therapy strategies for individuals with CVD.

NINDS is the lead Institute for stroke research at NIH, supporting a comprehensive portfolio that includes basic studies of disease mechanisms; epidemiology studies to assess risk, occurrence, and outcomes; clinical research to develop effective prevention and acute treatment approaches; and development of strategies for improving

[449] Zhang D, et al. *Biomaterials*. 2013; 34(23):5813–20. PMID: 23642535.
[450] Marshall LM, et al. *Circ Res*. 2013;113(10):1159–68. PMID: 24036495.
[451] Zangi L, et al. *Nat Biotechnol*. 2013;31(10):898–907. PMID: 24013197.
[452] https://www.sprinttrial.org/public/dspHome.cfm.

recovery and rehabilitation in stroke patients. Clinical trials represent a large portion of NINDS' stroke research portfolio and have led to significant advances with impacts on patient care.

Following a recommendation from the 2012 NINDS Stroke Research Priorities Meeting, NINDS recently has established a national Stroke Trials Network[453] to more efficiently develop, promote, and conduct high-quality, multisite clinical trials to test promising interventions in stroke prevention, treatment, and recovery. Through prioritization of research questions, harmonization and sharing of data collected in trials, and research training opportunities, the interdisciplinary network will provide expertise and infrastructure for NIH-sponsored stroke clinical trials and build research capabilities that match scientific opportunities across the spectrum of stroke research.

Other NIH ICs also support CVD research. NICHD supports studies of preeclampsia, a potentially fatal complication of pregnancy in which a woman's blood pressure unexpectedly spikes to dangerously high levels with signs of damage to another organ system, notably the kidneys. Preeclampsia affects about 5–7 percent of pregnancies worldwide and is a major cause of both maternal and fetal illness and death. NIBIB supports a group of interdisciplinary researchers working to develop a new method of mechanical circulatory support and a mechanical heart that may eliminate the need for anticoagulant drugs. Using cutting-edge simulation techniques to understand the blood flow through these devices and a technology called the Device Thrombogenicity Emulator to validate their method, the team will work with manufacturers to improve the design of these mechanical devices.[454, 455] Improved designs will lead to the elimination of difficult and costly anticoagulant drug therapy and pave the way for long-term use of these mechanical devices, ultimately saving countless lives and reducing health care costs.

Other studies are comparing the effectiveness of available treatments. For example, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial supported by NINDS sought to determine whether opening narrowed brain arteries with a stent system, in conjunction with aggressive medical management of risk factors, is better at preventing stroke than aggressive medical management alone in high-risk patients with symptomatic narrowing of a major brain artery. Primary results in 2011 demonstrated that medical management, coupled with highly effective risk reduction through aggressive medical care, was superior to surgical intervention due to a greater than expected risk of stroke from the stenting procedure.[456] The study team recently reported that the early benefit of aggressive medical management, compared with stenting, persisted for more than 30 months, with significantly fewer strokes and deaths in the group of patients who received medical management alone.[457] The results of the trial provide important information to clinicians and patients on the best strategies for managing risk of stroke in patients with narrowed brain arteries.

In 2013, researchers began to release the results of another large clinical trial, supported by NHLBI and NCCAM, that examined the efficacy of using chelation therapy to reduce CVD and prevent heart attacks. Chelation is a chemical process in which a substance is used to tightly bind molecules such as metals or minerals so they can be removed from the body. Chelation therapy with disodium ethylene diamine tetra-acetic acid (EDTA) has a decades-long history as a treatment for heavy metal poisoning; however, some practitioners have used it for treating coronary artery disease, exposing patients to potential risks without any proof of its effectiveness. The trial, which involved 1,700 patients, showed a modest reduction in cardiovascular events for adults age 50 and older who had suffered a prior heart attack.[458] However, the results from a secondary analysis of the trial data suggest that the chelation treatments produced a marked reduction in cardiovascular events and death in patients with diabetes, but not in those without diabetes.[459] Addressing CVD in people with diabetes is an important public health challenge, and better treatment options are required. Because this study was not designed to discover how or why chelation might benefit patients with diabetes, further investigation

[453] https://www.nihstrokenet.org/.
[454] Girdhar G, et al. *PLoS One*. 2012;7(3):e32463. PMID: 22396768.
[455] Rowley JW, et al. *Circ Cardiovasc Interv*. 2012;5(2):296–304. PMID: 22511738.
[456] Chimowitz MI, et al. *N Engl J Med*. 2011;365(11):993–1003. PMID: 21899409
[457] Derdeyn CP, et al. *Lancet*. 2014;383(9914):333–41. PMID: 24168957
[458] Lamas GA, et al. *JAMA*. 2013; 309(12):1241–50. PMID:23532240.
[459] Escolar E, et al. *Circ Cardiovasc Qual Outcomes*. 2014;7(1):15–24. PMID: 24254885

is needed. Thus, NCCAM is exploring the possibility of a follow-up study in collaboration with several other NIH ICs.

NIDDK supports research on CVD as a common and devastating comorbidity of diabetes, obesity, and kidney disease. Clinical and basic studies are aimed at identifying and understanding factors and mechanisms that contribute to cardiovascular damage in these diseases, while clinical prevention trials are aimed at finding strategies to prevent CVD in people at risk. For example, the Look AHEAD (Action for Health in Diabetes) clinical trial, funded by NIDDK and other NIH ICs, was designed to determine whether an intensive lifestyle intervention aimed to promote weight loss could improve health outcomes in people who have obesity and type 2 diabetes. After nearly 10 years of follow-up investigation, the numbers of CVD events were not significantly different between the intensive lifestyle intervention group and the diabetes support and education group. However, participants in the lifestyle intervention group lost significantly more weight and better maintained their lost weight than those in the control group. Furthermore, the lifestyle intervention group showed improved fitness, glucose control, and blood pressure, with less use of medication, and other health benefits.[460]

NIDDK also is leveraging landmark diabetes clinical trials through follow-up studies that can reveal the long-term effects of trial interventions on the development of CVD and other health outcomes. Already, one such study, the Epidemiology of Diabetes Interventions and Complications Study, a follow up to the NIDDK's landmark Diabetes Control and Complications Trial, has shown that tight glucose control prevents or delays the cardiovascular complications of type 1 diabetes. The SEARCH for Diabetes in Youth study, which is jointly led by NIDDK and CDC, also found that youth with type 1 diabetes showed signs of CVD risk, even early in the course of the disease.[461, 462] Similarly, the Diabetes Prevention Program (DPP) Outcomes Study, a long-term follow up to the landmark DPP clinical trial, has found that the DPP lifestyle intervention significantly improved long-term markers of cardiovascular health. Another large scale effort, the Chronic Renal Insufficiency Cohort (CRIC) study, co-sponsored by NIDDK and NHLBI, is evaluating long-term cardiovascular risk and outcomes in people with CKD. CRIC researchers have observed deterioration in heart function as patients progress from advanced kidney disease to kidney failure.[463]

Stroke research continues to make considerable advances, but challenges remain that current and future research efforts will need to overcome. At the NINDS Stroke Research Priorities Meeting in August 2012, leaders from the research community identified top priorities for stroke prevention, treatment, and recovery research. High-priority research topics identified included development of new or improved neuroprotection and reperfusion therapies, improved understanding of small vessel disease and its contribution to incident stroke and to vascular cognitive impairment, and improved validity and predictability of preclinical stroke research. Disparities in stroke risk and burden also continue to be a major challenge, and NINDS is coordinating a separate effort to identify future research needed to develop effective strategies to address the disproportionate burden of stroke experienced by minority groups.

Chronic Obstructive Pulmonary Disease

COPD is a serious but largely preventable lung disease that makes breathing difficult and is the third most common cause of death in the U.S. The disease has two forms, emphysema and chronic obstructive bronchitis, that tend to coexist in most people with COPD. More than 12 million Americans are currently diagnosed with COPD, and researchers estimate that 12 million more Americans have it but do not know that they do. Doctors diagnose COPD using a simple breathing test called spirometry that measures how well the lungs are working. COPD symptoms include chronic shortness of breath, a cough with mucus production, and wheezing. Smoking is the leading cause of COPD in the U.S., but genetic and environmental factors such as air pollution also play a role.

Significant and ongoing research investments by NIEHS are directed at uncovering the relationships between exposure to certain environmental agents (e.g., ozone, particulate

[460] Look AHEAD Research Group. *N Engl J Med*. 2013;369(2):145–54. PMID: 23796131.
[461] Jaiswal M, et al. *Diabetes Care*. 2013;36:157–162. PMID: 22961570.
[462] Urbina EM, et al. *Diabetes Care*. 2013;36: 2597–9. PMID: 23564920.
[463] Bansal N, et al. *Clin J Am Soc Nephrol*. 2013.;8(3):355–62. PMID 23411431.

matter, endotoxins, excessive heat) and cardiopulmonary disease. One study is using individual exposure assessment and disease-specific health outcomes to understand future health effects of extreme heat, which are projected to increase with climate change, on highly vulnerable populations with COPD and asthma. Although outdoor air pollution has known adverse effects on COPD morbidity and mortality, the indoor environment is of particular concern because most people spend the majority of their time indoors. One study is looking at whether the placement of portable air cleaners in homes of people with COPD can improve respiratory symptoms, lung function, and quality of life.

Researchers are making important strides toward understanding the effects of cigarette smoking on the development of COPD. NHLBI-funded investigators found that a major pathway of emphysema progression is through the apoptosis, or programmed cell death, of alveolar epithelial cells in response to cigarette smoke–mediated oxidative stress.[464] Other investigators found that transforming growth factor beta (TGF-beta) activated in patients with COPD and in animals exposed to cigarette smoke induces alveolar apoptosis and emphysema, suggesting that inhibition of the TGF-beta pathway, possibly through the use of the medication losartan, might be a potential therapy for COPD.[465]

Because COPD involves a wide range of abnormalities, different patients with COPD may require specific treatments. Characterizing the different subtypes of COPD is a critical first step toward personalizing treatment approaches. The COPDGene Study is evaluating 10,000 current and former smokers, with and without COPD, to improve categorization of the various abnormalities seen on x-ray computed tomography (CT) lung images and to identify genetic traits that are associated with specific manifestations of the disease. Recent GWAS, for example, have identified susceptibility regions on chromosomes 19[466] and 15.[467] These investigators also recently have demonstrated that high-resolution CT of the lung can facilitate the identification of certain lung pathologies well before the onset of symptoms and before irreversible damage has occurred.[468] The comprehensive clinical, imaging, and genetic data obtained from this study can be used to provide clinicians with more accurate prognoses and enable the development of targeted, personalized, and more effective therapies to preempt chronic disease.

NHLBI's Lung Genomic Research Consortium is performing state-of-the-art high-throughput molecular analyses of lung tissues removed from patients with COPD to find molecular "fingerprints" that indicate different subtypes of the disease as well. For example, SPIROMICS (the SubPopulations and InteRmediate Outcome Measures in COPD Study) will define subpopulations of COPD patients by extensive molecular and clinical phenotyping and also will identify intermediate outcome measures that can be used to improve the efficiency of future clinical trials. Another group of researchers found that pulmonary artery enlargement as detected by CT is a predictor of future exacerbations in COPD patients and may provide a practical tool to identify a COPD subpopulation at high risk for hospitalization.[469]

A number of recent studies are pointing toward better medical approaches for treating COPD. For example, investigators recently found that a broccoli sprout derivative, sulforaphane, was found to potentially augment the anti-inflammatory effects of steroids in COPD.[470] Promising therapeutic leads also are being pursued through the NHLBI Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases (CADET), the first stage of which concluded in 2013. The goal of CADET is to accelerate the development of novel agents for the diagnosis and treatment of lung diseases like COPD by providing support for validation of potential targets and developing novel therapeutics.

Large, multicenter clinical trials are evaluating the efficacy of several treatments or therapies that are available for immediate use. The NHLBI-supported Long-term Oxygen Treatment Trial is testing the ability of supplemental oxygen treatment to prevent deaths and hospitalizations in patients with COPD and less-than-severe hypoxemia (oxygen

[464] Kamocki K, et al. *Am J Respir Cell Mol Biol*. 2013;48(1):87–93. PMID: 23024063.
[465] Podowski M, et al. *J Clin Invest*. 2012;122(1):229–40. PMID: 22182843.
[466] Cho MH, et al. *Hum Mol Genet*. 2011;21(4):947–57. PMID: 22080838.
[467] Wilk JB, et al. *Am J Resp Crit Care Med*. 2012;186(7):622–32. PMID: 22837378.
[468] Galban CJ, et al. *Nat Med*. 2012;18(11):1711–5. PMID 23042237.
[469] Wells J, et al. *N Engl J Med.* 2012;367(10):913–21. PMID: 22938715.
[470] Malhotra D, et al. *J Clin Inv*. 2011;121(11):4289–302. PMID: 22005302.

deficiency). A trial conducted by NHLBI's COPD Clinical Research Network is testing whether simvastatin, a drug approved for CVDs, can be used to reduce the frequency of COPD exacerbations.

COPD patients often suffer from multiple afflictions. Therefore, NIH supports research aimed at understanding these comorbidities. For example, in 2012 NHLBI launched the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study that is aimed at understanding the molecular mechanisms that underlie the susceptibility of alpha-1 antitrypsin-deficient subjects to the development of COPD. Similarly, lung cancer occurs 4–5 times more frequently in COPD patients than in smokers without COPD. To investigate the cellular and molecular mechanisms that contribute to both COPD and lung cancer, NHLBI and NCI have awarded seven grants to promote research on the connections between these lung diseases, which together cause more than 250,000 deaths in the U.S. each year.

Because COPD accounts for more than 300 million patients worldwide, NHLBI is participating in discussions with WHO and other international groups about strategies for dealing with COPD at the global level. COPD surveillance data are being collected in developing countries through the NHLBI Centers of Excellence in Global Health. In addition to smoking, indoor air pollution contributes to COPD risk on a global level.

Chronic Pain and Palliative Care

Chronic pain is now viewed as a chronic disease condition in the same way as other chronic diseases covered in this section, such as diabetes and asthma. By its nature, chronic pain persists over a long period of time and is resistant to many medical treatments. It can—and often does—cause severe problems, hugely impacting quality of life for an individual. The term *palliative care* describes medical care for people suffering from serious illnesses, focusing on providing relief from the symptoms, such as pain, to improve quality of life.

Chronic Pain

Many chronic diseases are associated with pain that can be both chronic and severe. Chronic pain also can be a disease in itself—for example, in conditions such as fibromyalgia, migraine, interstitial cystitis, and vulvodynia. Chronic pain often is difficult to treat and can significantly erode quality of life. NIH supports a spectrum of pain research (also discussed in the "Neuroscience" section in this chapter) that includes both basic science—to understand the mechanisms of acute and chronic pain and pain relief, pain as a biopsychosocial condition, and the risk factors for developing chronic pain—and clinical research—to evaluate pharmacologic and other strategies for pain management.

Chronic pain is a debilitating symptom of many long-term disease states, such as cancer or arthritis. It also may manifest as a persistent pain state that outlasts an acute injury or illness or arises in the absence of an identified causative mechanism. Persistent pain is widely considered to be a distinct disease state in itself. The transition from acute pain to a persistent and intractable pain condition involves improper functioning of neuronal pain circuits in which parts of the nervous system become hypersensitized for long or indefinite periods of time. It is unclear why some, but not all, people develop chronic pain after an acute insult has resolved. Common chronic pain conditions include migraine and other headaches; low back pain; cancer pain; arthritis pain; and neuropathic pain, such as in diabetic neuropathy (pain resulting from disease-related damage to the peripheral nerves or CNS).

Many chronic pain conditions are comorbid or overlapping in nature, with two or more conditions occurring simultaneously in the same patient. Some of these overlapping disorders likely share common mechanisms, including genetic susceptibility and changes in the nervous and immune systems as well as in inflammatory processes. Overlapping pain conditions may include migraine, chronic fatigue syndrome (CFS), endometriosis, fibromyalgia, irritable bowel syndrome (IBS), interstitial cystitis/painful bladder syndrome, temporomandibular joint disorders, uterine fibroids, and vulvodynia. Chronic pain conditions can be exacerbated by environmental or psychosocial factors.

NIH Chronic Pain Research Activities

NIH funds a broad portfolio of chronic pain research activities ranging from basic research into the molecular, genetic, and biobehavioral basis of chronic pain to large-scale clinical studies of potential treatments. A number of trans-NIH or Common Fund programs support chronic pain research, reflecting shared interests across NIH in different aspects of chronic pain research, such as understanding the simultaneous occurrence of multiple chronic pain conditions and the factors that put some individuals at risk. The NIH Blueprint for Neuroscience Research funds cutting-edge mechanistic pain research through the Blueprint Grand Challenge for Pain, as well as projects aimed at analgesic drug development through the Blueprint Neurotherapeutics drug development program. A multi-Institute program for Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) for Neuroscience and Disorders of the Nervous System funds innovative pain research, and NIH also supports basic and translational pain research through its small business research programs. Common Fund support for pain research includes projects awarded through the Transformative Research Award Program and the Health Care Systems Research Collaboratory, an effort to develop resources and infrastructure for large-scale pragmatic trials. One of two large "real-world" clinical trials on chronic pain funded through the Collaboratory will determine whether integrated and multimodal pain management benefits people with various pain conditions in terms of pain relief, reduced opioid use, and lower costs.[471]

In addition to trans-NIH efforts, NIH ICs fund chronic pain research aligned with their missions through FOAs, workshops, and conferences. Mission-relevant research at NINDS focuses on headache, neuropathic pain research, and understanding the neurobiological mechanisms of many pain conditions that result from injury or disease of the nervous system. NINDS is funding a 10-year study on overlapping pain conditions that disproportionately affect women, including episodic migraines, as well as a comparative effectiveness trial of drugs used to prevent pediatric migraine. Results are expected to have a significant effect on clinical practice and could help to establish clinical practice guidelines for headache management in children and adolescents.

NIDCR-supported scientists are studying a common disorder of the jaw area called temporomandibular joint and muscle disorder (TMD), which affects thousands of Americans each year.[472] Studies on TMD and other orofacial pain conditions range from basic pain mechanisms to clinical trials. For example, NIDCR scientists are investigating inflammation of the temporomandibular joint associated with TMD and how this can result in activation of pain pathways.[473] In the area of clinical research, NIDCR supports the Orofacial Pain: Prospective Evaluation and Risk Assessment Program (OPPERA), a longitudinal study aimed at identifying a set of risk factors for the first onset of TMD, as well as risk factors for the development of chronic TMD. The first phase of OPPERA identified several risk factors in 2011,[474] and the second phase of this study (OPPERA II), initiated in August 2012, will identify similar sets of risk factors as well as genetic factors that determine risk for the transition from acute to chronic TMD and risk factors for TMD cases that will develop additional chronic pain conditions.

In 2013, in partnership with 11 other ICs, NINR issued a FOA to foster a wide range of basic, clinical, and translational studies on pain from the micro perspective of molecular sciences to the macro perspective of behavioral and social sciences. NINR also sponsors research and training opportunities to improve research capacity in the science of pain, such as its intramural NINR Symptom Research Methodologies Series, a one-week intensive research training course held at NIH. The purpose of the course is to increase the research capability of graduate students and faculty, and topics have included research methodologies for such symptoms as pain, sleep deprivation, and fatigue.

Other NIH ICs support pain research as well. In 2012, NIA led a trans-NIH initiative to support research on pain from an aging perspective, including studies of older populations, studies of age differences and age-related changes in pain processes and experiences, and studies of pain

[471] More information on these Common Fund Programs can be found at http://commonfund.nih.gov/TRA and http://commonfund.nih.gov/hcscollaboratory/index/.

[472] Roda RP, et al. *Med Oral Patol Oral Cir Bucas*. 2007;12:E292–8. PMID: 17664915.

[473] Prochazkova M, et al. *Mol Pain*. 2013; 9:66.PMID: 24359609.

[474] Fillingim, RB, et al. *J Pain*. 2011;12(11, Suppl. 3): T102–7. PMID: 22074748.

Figure 3-10. *Graduate nursing students and nursing faculty attending the NINR Symptom Research Methodologies Series "Boot Camp." Credit: NINR.*

treatment and management in older adults. In addition, two NCCAM-funded Centers of Excellence for Research on Complementary and Alternative Medicine used advanced functional and structural neuroimaging technologies to study pain and the effect of mind-and-body interventions.

Coordination of Pain Research

NIH plays a key role in the Interagency Pain Research Coordinating Committee (IPRCC),[475] created to enhance pain research efforts and promote collaboration across the government, advance fundamental understanding of pain, and improve pain-related treatment strategies. The IPRCC includes biomedical researchers, representatives from nonprofit public advocacy organizations, and representatives of six federal government organizations that deal with pain research and patient care. The Committee has completed an extensive analysis of the federal pain research portfolio, identified recent science advances that have made significant contributions to the field, and undertaken the National Pain Strategy to address a key recommendation of the IOM committee: develop a nationwide population level plan to improve pain research, education, prevention, and management.

[475] http://painconsortium.nih.gov/.

Pain research activities at NIH are coordinated in large part by the NIH Pain Consortium, a joint undertaking across 25 ICs and Offices that identifies and facilitates implementation of key opportunities in collaborative pain research. In 2012–2013, the Consortium coordinated a number of pain research initiatives and activities at NIH, which included developing research standards and tools for research on low back pain, recommending objectives to enhance research on overlapping chronic pain conditions such as migraine and temporomandibular joint disorders, establishing clinical training curriculum tools in pain education, and supporting a collaboration with Stanford University for a nationwide pain patient data registry. For example, in 2012, NCCAM and NIAMS coordinated a Pain Consortium Task Force that developed research standards for chronic low back pain.[476] The Consortium also continues its efforts to identify key opportunities in pain research and education, convene conferences and workshops to highlight recent advances and needs in the field, and build collaborations with other federal agencies, such as FDA, and academic institutions involved in pain research. NINDS, as the lead Institute for pain research at NIH, established the Office of Pain Policy in 2012 to support and coordinate the increasing activities of the NIH Pain Consortium and the IPRCC. The Office is a key player in developing the National Pain Strategy and has developed a database of pain research supported by federal agencies.[477]

Advances and Priorities in Chronic Pain Research

NIH's significant investment in pain research recently has provided important advances in our basic understanding of pain and our ability to treat it. For example, the ability to use brain imaging methods to predict who is at risk for developing chronic low back pain and who will recover after an acute injury may help to optimize treatment strategies.[478] Brain imaging studies supported by NIH also revealed the role of certain brain circuits in pain perception.[479] In particular, scientists identified a neurological signature that is specific and sensitive to physical pain using functional MRI. These studies may help to provide more standardized, reproducible, and less subjective measures of pain, which could facilitate the development of more individualized and better treatments. NIH-funded researchers have determined, at near-atomic resolution, the structure of a protein that plays a central role in the perception of pain and heat.[480] A follow-up study shows how the protein changes when bound to substances that trigger severe pain.[481] This key research contributes significantly to the field of structural biology and offers insights to better design of drugs for pain treatment.

Understanding and managing chronic pain is hampered by the neurobiological and psychosocial complexity of the conditions and by the individual variation in susceptibility to chronic pain, perception of pain, and response to pain therapies. One challenge to therapy development for pain conditions has been that results from studies using animal models have predicted outcomes poorly in clinical research. Therefore, efforts are underway to improve animal models and assays for pain to better reflect the complexity and features of chronic pain conditions in people. Priorities for advancing pain research include understanding how acute pain transitions to chronic pain, identifying biological pain signals, determining the risks and predictors of who will develop one or more chronic pain conditions, who will respond to certain therapies, the benefits of integrated and interdisciplinary pain care, and developing alternative pain medications with reduced abuse liability.

Advancing understanding of pain and pain relief through complementary and integrative health approaches is another priority for NIH pain research. NCCAM IRP is dedicated to the study of the brain's perception of pain, and a large portion of NCCAM's extramural portfolio is committed to the study of the nonpharmacological management of pain, such as through the use of acupuncture, chiropractic, massage, meditation, and relaxation techniques. For example, a meta-analysis of individual patient data on use of acupuncture for four chronic pain conditions found it effective for treatment of chronic pain, a reasonable referral option, and more than a placebo. However, modest differences when compared to a control (sham acupuncture) group suggest that other factors in addition to needling may contribute to acupuncture's therapeutic effects.[482]

[476] http://painconsortium.nih.gov/NIH_Pain_Programs/Task_Force/cLBP_RTF_FullReport.pdf.
[477] http://paindatabase.nih.gov.
[478] Baliki MN, et al. *Nat Neurosci*. 2012;15(8):1117–9. PMID: 22751038.
[479] Wager TD, et al. *N Engl J Med*. 2013 Apr 11;368(15):1388–97. PMID: 23574118.
[480] Liao M, et al. *Nature*. 2013;504(7478):107–12. PMID: 24305160.
[481] Cao E, et al. *Nature*. 2013;504(7478):113–8. PMID: 24305161.
[482] Vickers AJ, et al. *Arch Intern Med*. 2012;172(19):1444–53. PMID: 22965186.

NIH also convened a number of conferences, workshops, and strategic planning efforts on chronic pain conditions in 2012–2013. For example, in August 2012 the NIH Pain Consortium hosted the Chronic Overlapping Pain Conditions Workshop.[483] Also in May 2012 and 2013, the Pain Consortium's *7th* and *8th Annual Symposia on Advances in Pain Research* were held on the NIH campus. The 2012 symposium focused on advances in the development of novel pain therapies, and the 2013 symposium highlighted integrated self-management strategies for chronic pain. This yearly symposium helps the Pain Consortium in its mission to develop a comprehensive and forward-thinking pain research agenda for NIH, identify key opportunities in pain research, and foster multidisciplinary and trans-NIH initiatives.

Chronic Pelvic Pain

Chronic pelvic pain is a general term that health care providers use to describe pain that occurs mostly or only in the lower abdominal area. The pain may be steady or recurrent and includes conditions affecting and/or originating in the genitourinary and GI tracts. Common health conditions associated with chronic pelvic pain include interstitial cystitis/painful bladder syndrome (IC/PBS), which is pelvic pain strongly associated with the bladder and with urinary symptoms of frequency and urgency; chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), which is prostate pain seemingly due to inflammation, but in the absence of bacteria and even, sometimes, of host inflammatory cells in urine or prostatic fluid; vulvodynia, which is chronic pain or discomfort of the vulva; endometriosis, a condition that occurs when tissues that usually line a woman's uterus instead grow outside the uterus; uterine fibroids, which are common, noncancerous tumors that grow within and around the wall of the uterus; and IBS, a functional GI disorder with symptoms that include abdominal pain.

NIH supports a wide range of basic, clinical, and translational research to better understand the causes of chronic pelvic pain conditions and to find ways to diagnose, prevent, treat, and possibly cure them. IC/PBS, CP/CPPS, vulvodynia, and IBS are especially challenging pain conditions because their cause(s) are unknown and fully effective treatments remain elusive.

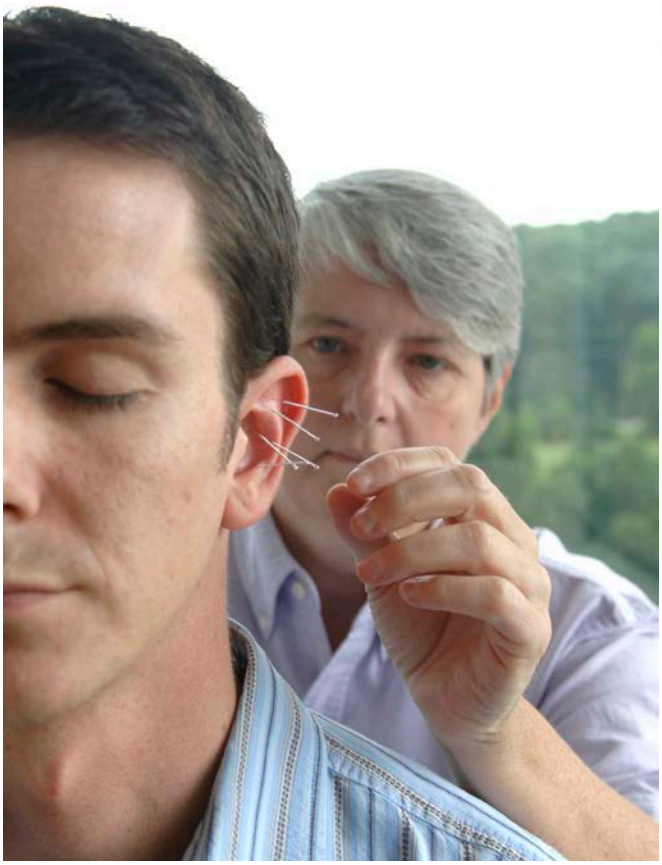


Figure 3-11. *An acupuncturist inserts needles into a man's ear. Credit: ©Bob Stockfield, courtesy of NCCAM.*

NIDDK supports studies to address chronic pelvic pain of urologic and GI origin, including the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. This network includes multiple centers to conduct innovative, collaborative studies of IC/PBS and CP/CPPS that include searching "beyond the bladder/prostate" to find the causes of these conditions and includes studies of the possible relationships between these conditions and other chronic pain disorders, such as IBS and fibromyalgia. NIDDK, with co-funding from ORWH, is planning to support and enhance the MAPP Research Network for a second five-year phase so that these important studies can continue.[484]

[483] http://painconsortium.nih.gov/Conferences_and_Seminars/Chronic-overlapping-pain-conditions-workshop.pdf.

[484] http://rt5.cceb.upenn.edu/mapp_web/MAPP_About.html.

In treatment research, an NIDDK-supported clinical trial found that a physical therapy regimen, called myofascial physical therapy (MPT), targeting muscle and connective tissue in the pelvic floor, hip, and abdominal areas helped improve symptoms in women with IC/PBS more than whole-body therapeutic massage. Researchers can now pursue such questions as the durability of treatment effects and which patients are most likely to benefit from treatment, as well as other issues that could help determine whether pelvic MPT could become a standard clinical treatment for women with IC/PBS.[485]

To study the possible role of estrogen in the pain symptoms of IC/PBS, NIDDK-supported researchers used a specific mouse model of IC/PBS, called a "neurogenic cystitis" model, that recapitulates pelvic pain symptoms seen in humans and also is thought to be one possible pathway for how IC/PBS develops in humans. Their findings suggest that in this model, sex differences in pelvic pain exist, but are not dictated by estrogen; genetic differences play a role in determining susceptibility to pelvic pain; and the two may be related. Further study of sex differences and the role of genetics in pelvic pain could have important implications for understanding IC/PBS pain in people.[486]

The Women's Health and Functional Visceral Disorders Center is studying the interplay between gut and brain pathways in IC/PBS and IBS, focusing on sex differences in the development, clinical manifestation, and treatment response in these pain syndromes. This interdisciplinary Specialized Center of Research on Sex Differences was established through an ORWH program and is co-funded by NIDDK and ORWH.[487] Results from a randomized, controlled clinical trial conducted by Center researchers showed improvement in symptoms among women and men with IBS following a five-week course of group therapy involving psychological and educational approaches emphasizing self-efficacy and practical relaxation techniques; the therapy was particularly helpful for those individuals who had a low or average quality of life before starting the intervention. This study demonstrated an effective, low-cost method of treating IBS symptoms and could pave the way for the adoption of such an approach as an alternative to, or a supplement for, pharmacological therapy.[488]

NIDDK supports fundamental studies of the bladder and prostate in health and disease, including studies of structure, function, and innervation, as well as studies of the possible role of infectious agents in triggering urologic pain. NIDDK also supports fundamental studies of GI innervation, motility, and bacterial complement that could provide insight into why and how IBS develops.

NICHD also supports research on chronic pelvic pain disorders. For example, the Pelvic Floor Disorders Network is a highly productive clinical trials network that conducts research on how to improve the care and daily lives of women with pelvic organ prolapse and bladder and bowel control problems. NICHD and ORWH are also co-funding a clinical trial to investigate the efficacy of the drug gabapentin in vulvodynia treatment as well as to identify clinical features associated with successful treatment response.

Endometriosis, another pelvic pain disorder, occurs when tissues that usually grow inside the uterus instead grow on the outside, such as on the surfaces of organs in the pelvis or abdomen. Endometriosis may cause infertility or pelvic pain and affects an estimated 8–10 percent of reproductive-age women. The pain of endometriosis can be chronic or cyclical. Researchers surveyed women enrolled in an endometriosis research program registry in Puerto Rico to study the burden of disease from a patient perspective. The majority of survey respondents indicated that their pain interfered with daily activities, and about 66 percent reported that their pain interfered with work. Respondents who missed work due to pain were absent an average of 2.8 days per month. Among all respondents, endometriosis resulted in an average of 19.3 days of work missed per year. Thus, for women with moderate to severe cases, the burden of endometriosis significantly impacts quality of life across home, work, and social domains. These effects are costly not only to the patients, but also to the medical system and employers.[489] Recently, investigators with NICHD

[485] FitzGerald MP, et al. *J Urol*. 2012;187(6):2113–8. PMID: 22503015.
[486] Rudick CN, et al. *J Urol*. 2012;187(2):715–24. PMID: 22177208.
[487] http://orwh.od.nih.gov/sexinscience/researchtrainingresources/scor.asp.
[488] Labus J, et al. *Aliment Pharmacol Ther*. 2013;37(3):304–15. PMID: 23205588.
[489] Fourquet J, et al. *Fertil Steril*. 2010;93(7):2424–8. PMID: 19926084.

support have been able to induce endometriosis lesions in experimental mice and then significantly reduce the lesions by treating the animals with all-trans-retinoic acid, a nutrient the body makes from vitamin A that is known to have an anti-inflammatory effect.[490]

NICHD and ORWH also fund a study that aims to develop a new nonsteroidal treatment for endometriosis by examining the mechanisms by which inhibitors of specific prostaglandin receptors relieve endometriosis pain and prevent disease progression. In addition, NIH also sponsors conferences to stimulate innovative research and encourage collaboration on pelvic pain disorders. In 2013, for example, The World Endometriosis Society Montpellier Consortium, in which NICHD participates with an international group of clinical and research experts and women with this condition, published the first-ever worldwide consensus statement on the management of this painful disorder.[491]

Uterine fibroids may cause painful menstrual periods, heavy bleeding, pain during sexual intercourse, infertility, anemia, and fatigue. One study estimated that one of four American women—and up to three of four African-American women—has uterine fibroids that cause problematic symptoms. Although scientists know that the female hormones estrogen and progesterone play a role in the growth of fibroids, they have been unable to determine what causes uterine fibroids to develop. NIEHS-led studies are attempting to answer this question. The Fibroid Growth Study examines the variation in fibroid growth, the biological differences between growing and nongrowing fibroids, and the relationship between fibroid growth and symptom severity. The Study of Environment, Lifestyle, and Fibroids is using ultrasound to screen African-American women who have not had fibroids to determine what may trigger the condition.

Treatment options for uterine fibroids are limited to hormone therapy and surgery. However, hormone therapies used to treat fibroid tumors do not always produce much improvement and only temporarily relieve symptoms. Even if fibroids are surgically removed, they may return or their removal may result in the formation of painful scar tissue. The only sure way to prevent fibroids from returning is to remove the uterus, which is not an option for women who want to have children in the future.

Researchers are investigating new treatments for fibroids with the hope of finding an option that will provide long-term relief without compromising fertility. One possibility is treatment with a drug that is known to be effective in treating the skin diseases ichthyosis and psoriasis by blocking a particular metabolic pathway known to affect cell growth and differentiation. With NICHD support, researchers investigated the effects of this drug, liarozole, on genes known to create the fibrosis (excessive formation of fibrous connective tissue) that is the main cause of fibroid symptoms. They found that when the drug was administered at pharmacologic concentrations, it decreased the ability of fibroid cells to multiply.[492]

Palliative Care

Palliative care, which includes pain management, focuses on alleviating disease symptoms and improving patients' quality of life. Optimizing end-of-life care is an important topic within the field of palliative care research, particularly with respect to understanding the needs of dying children with chronic diseases, older people, and their families. Researchers are also studying the many cultural, spiritual, age-related, and disease-specific factors that affect the end of life. Because each person's experience at the end of life is unique, NIH has developed an initiative to support research on interventions for end-of-life and palliative care (EOL PC) that can be applied in a variety of settings, illnesses, and cultural contexts.

EOL PC science develops strategies to prevent, reduce, or comfort the symptoms of advanced illness. It includes management of pain and other symptoms and emotional, social, spiritual, and informed decision-making support. Interventions address supportive, palliative, and hospice needs across a continuum of services in coordination with

[490] Weiser F, et al. *Fertil Steril*. 2012:96(6):1430–7. PMID: 22464761.
[491] Sasao H, et al. *Int Heart J.* 2013;54(1):1–6. PMID: 23428916.
[492] Gilden M, et al. *Fertil Steril*. 2012;98(6):1557–62. PMID 22925684.

individuals, families, and their health care teams. Science advances from NINR EOL PC research include:

- Clinician-patient discussions about preferences for life-sustaining treatments could reduce unwanted treatments at the end of life.
- Improving communication and providing decision support helps parents making difficult decisions regarding the care of their children who have life-threatening illnesses.

As the lead NIH Institute for end-of-life research, NINR supports science to assist individuals, families, and health care professionals in managing the symptoms of life-limiting conditions and planning for end-of-life decisions. The Office of End-of-Life and Palliative Care Research within NINR coordinates and supports ongoing NINR and NIH research efforts in EOL PC science, including:

- Stimulation of EOL PC research initiatives
- Creation of opportunities for collaborative activities
- Facilitation of interdisciplinary EOL PC science
- Identification of opportunities for science to inform policy and practice

A major program priority is to coordinate the development, implementation, and evaluation of EOL PC research in direct collaboration with other NIH ICs, federal research agencies, and outside constituencies.

NINR developed the Palliative Care: Conversations Matter® campaign to raise awareness of pediatric palliative care and to help health care professionals and patients discuss palliative care earlier. Health care professionals may have difficulty talking about palliative care with their patients—particularly with children. Many patients and their families have never heard of palliative care, and they are not aware that it can give them extra support in dealing with a serious illness. This is especially true when talking about palliative care for children. To develop the Palliative Care: Conversations Matter® campaign, NINR brought together parents and palliative care clinicians, scientists, and professionals to give their input and expertise on what they thought was needed in the field. The Institute pilot tested the health care provider campaign materials for nine months in two health care systems to gather feedback from an interdisciplinary group of health care providers. NINR hopes that this campaign will increase the use of palliative care for children living with serious illnesses or life-limiting conditions.

Mental Illness

Mental illnesses are major chronic diseases in our country, affecting millions of people, young and old. New initiatives will seek to change the treatment paradigm from one of treating chronic illness to one of preempting the illness long before symptoms emerge. NIMH has two landmark studies to build upon: The North American Prodrome Longitudinal Study is a consortium of clinical research centers studying ways to identify individuals earlier who are at risk for an initial psychotic episode. Through this study, we have the opportunity to create a toolkit to improve prediction of psychosis using biosignatures and neurocognitive testing. The Recovery After an Initial Schizophrenia Episode (RAISE) project[493] is a large-scale research effort to explore whether using early and aggressive treatment will reduce the symptoms for individuals who already have had a psychotic episode and prevent the subsequent gradual deterioration of functioning. RAISE will be expanded with the aim to reduce the duration of untreated psychosis by linking community mental health care to primary care and school mental health resources.

Eating disorders also are often chronic, relapsing illnesses that typically develop during the mid-teens to early adulthood. People with eating disorders often have coexisting psychiatric illnesses, including anxiety, mood, and substance use disorders (SUD). In addition, a wide variety of medical complications associated with eating disorders have been identified. For anorexia nervosa, these medical complications and a high suicide rate result in a mortality rate that is among the highest for mental disorders.[494] NIMH continues to invest in research that helps to clarify the neurobiological mechanisms that underlie the behavioral dysregulation found among eating disorders; identify biological, environmental, and genetic risk factors; and improve interventions.

[493] http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml.
[494] Arcelus J, et al. *Arch Gen Psychiatry*. 2011;68(7):724–31. PMID: 21727255.

Obesity

Obesity[495] is a major contributor to serious health conditions in children and adults. Individuals who are obese have increased risk for type 2 diabetes, heart disease, stroke, many forms of cancer, osteoarthritis, liver disease, gallbladder disease, urinary incontinence (UI), sleep-disordered breathing, dementia, and many other diseases and conditions. Defined as an excess of body fat, obesity develops when the number of calories consumed in food and beverages exceeds the number of calories that the body burns to fuel basic life functions, physical activity, and normal growth during childhood. A complex interplay of factors influences obesity—from genetics and other aspects of our biology to chemical exposures and a range of other environmental factors to psychological and behavioral factors.

In 2011–2012, 34.9 percent of adults and 16.9 percent of children and adolescents were obese.[496] Given the alarming levels of obesity over the past three decades, NIH invests significantly in a broad portfolio of basic, clinical, and translational research to (1) understand the complex factors that regulate body weight and contribute to obesity; (2) test obesity prevention and treatment strategies for children and adults; and (3) build the evidence base to inform local and national policies. Many studies include racially/ethnically diverse and socioeconomically disadvantaged populations and populations in geographic areas burdened by obesity.

NIH research on obesity is guided by the NIH Obesity Research Task Force. In 2011, the Task Force developed an updated *Strategic Plan for NIH Obesity Research*, with extensive external input, framed around the following overarching themes:

- Discover fundamental biologic processes that regulate body weight and influence behavior.
- Understand the consequences of obesity and its contributing factors.
- Design and test new interventions for achieving and maintaining a healthy weight.
- Evaluate promising strategies for obesity prevention and treatment in real-world settings and diverse populations.
- Harness technology and tools to advance obesity research and improve health care delivery.
- Facilitate integration of research results into community programs and medical practice.

Basic research in obesity looks at numerous risk factors that may predispose an individual to obesity. Factors currently under investigation include genetic contributions; the role of gut microbes and how these microbes may be affected by different diets; circadian desynchronizations, such as sleep deficiency; the role of different types of fat tissue; developmental exposure to a variety of environmental chemicals, such as arsenic and bisphenol A; sex differences, as related to sleep, reproductive health, sex hormones, pregnancy, and so forth; psychosocial and behavioral factors, such as the role of social settings on food consumption; and research on the effects of policies and other environmental factors on physical activity and food choices (e.g., how nutritional information or costs of healthier and less healthy foods may affect purchasing patterns). With NIH support, scientists are investigating whether elevated maternal blood glucose during pregnancy (a less severe condition than gestational diabetes) may influence later levels of body fat in children as well as development of diabetes in mothers after giving birth.

Basic research findings indicate potential new approaches toward combating this rising epidemic. For example, recent research has found new brain inputs that help regulate satiety. In one study, ingestion of glucose, but not fructose, was shown in humans to activate brain pathways and stimulate hormones that promote feelings of satiety, fullness, and reward.[497] In a separate study in mice, oleoylethanolamine, a chemical produced in the gut, was shown to regulate the sense of satiety after dietary fat consumption by inducing dopamine release in the brain, a process that is disrupted after excessive high-fat feeding.[498] Another study in mice has found that gut microbes obtained

[495] Adults are considered to be obese when their body mass index is 30 kg/m^2 or higher.
[496] Ogden CL, et al. *JAMA*. 2014;311(8):806–14. PMID: 24570244.
[497] Page KA, et al. *JAMA*. 2013; 309(1): 63–70. PMID: 23280226.
[498] Tellez LA, et al. *Science*. 2013; 341(6147): 800–2. PMID: 23950538.

from obese or lean people, within certain dietary contexts, can transmit obesity or leanness to mice in the lab.[499]

Translational research in obesity capitalizes on these advances to provide new directions in preventing and treating obesity. For example, researchers have shown that in mice, experimentally increasing levels of the muscle-produced hormone irisin reduces obesity and improves glucose levels and that exercise induces muscle to produce irisin. Humans produce an identical hormone, suggesting that irisin is a candidate for potential therapeutic use to achieve health benefits similar to those of exercise.[500] Scientists found that damage to the hypothalamus—the area of the brain involved in regulating appetite—was observed in people who are obese and in rodents fed a high-fat diet.[501]

NIH invests significantly in clinical and post-clinical research to address obesity. Several of the intervention strategies being investigated focus on behavioral and environmental changes to foster healthier eating and physical activity in a variety of contexts, such as the home, schools, health care, and other community settings. Other strategies under study include medical or surgical interventions. For example, the NHLBI-led Overweight and Obesity Control at Worksites Trials tested whether environmental interventions in the workplace, in combination with individual lifestyle modification, can prevent or control overweight or obesity in adults. Some interventions were successful in preventing weight gain or weight loss, but the investigators identified a need for better interventions to maintain weight loss over time.[502]

The long-term effects of bariatric surgery are being examined through NIDDK's multicenter Longitudinal Assessment of Bariatric Surgery study. Scientists recently have found that adults who had gastric bypass surgery to lose weight had a significantly higher risk of alcohol use disorders 2 years after surgery compared with before surgery. The study results suggest that clinicians should be aware of the importance of monitoring for signs and symptoms of alcohol use disorders and consider counseling after bariatric surgery, particularly in patients who undergo gastric bypass.[503]

[499] Ridaura VK, et al. *Science*. 2013; 341(6150): 1241214. PMID: 24009397.
[500] Boström P, et al. *Nature*. 2012:481:463–8. PMID: 22237023.
[501] Thaler JP, et al. *J Clin Invest*. 2012;122:153–62. PMID: 22201683.
[502] Thorndike AN, et al. *Am J Prev Med*. 2012;43(1):27–33. PMID: 22704742.
[503] King WC, et al. *JAMA*. 2012;307:2516–25. PMID: 22710289.

Many NIH ICs are investing in research to address the alarming rise of obesity in children and youth. For example, an NIEHS funding program supports research on the role of environmental chemical exposures during development or other windows of sensitivity in weight gain, altered glucose/insulin sensitivity, and altered lipid metabolism that lead to obesity, type 2 diabetes, and metabolic syndromes. The National Collaborative on Childhood Obesity Research (NCCOR) is a joint effort of NIH, CDC, USDA, and the Robert Wood Johnson Foundation, with the goal of improving the efficiency, effectiveness, and application of childhood obesity research through enhanced coordination and collaboration. Since its formation in 2009, NCCOR members have published nearly 800 papers on obesity-related topics, and NCCOR develops and promotes products to help its members illustrate their research.

Several ongoing trials seek to prevent or treat childhood obesity. For example, randomized trials in the NHLBI-led Childhood Obesity Prevention and Treatment Research Consortium are testing interventions to prevent excess weight gain in nonoverweight youth and in those already overweight and/or to reduce weight in obese and severely obese youth by targeting preschoolers, preadolescents, or adolescents. In addition, NIDDK and other ICs are funding LIFE-Moms, a set of studies of lifestyle interventions for overweight and obese pregnant women designed to improve weight and metabolic outcomes for the women and their children. Looking at one important comorbidity of obesity, the NIDDK-supported Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial has demonstrated how difficult it is to treat type 2 diabetes in children. The challenges in effectively treating type 2 diabetes in youth highlight the need for effective prevention and treatment of obesity.[504, 505, 506, 507]

For young adults, the Early Adult Reduction of weight through Lifestyle intervention trials,[508] supported by NHLBI and NICHD, are testing behavioral approaches for weight control in young adults aged 18–35 who are at high risk for weight gain, including pregnant and postpartum women, community college or university students, and young adults

[504] TODAY Study Group. *Diabetes Care*. 2013;36(6):1735–41. PMID: 23704672.
[505] TODAY Study Group. *Diabetes Care*. 2013;36(6):1772–4. PMID: 23704677.
[506] TODAY Study Group. *Diabetes Care*. 2013;36(6):1758–64. PMID: 23704675.
[507] TODAY Study Group. *Diabetes Care*. 2013;36(6):1749–57. PMID:23704674.
[508] http://www.nhlbi.nih.gov/research/resources/obesity/trials/early.htm.

trying to quit smoking. Interventions are delivered using technologies such as smartphones, social networking sites, Bluetooth-enabled scales, and text messages.

Researchers are examining community-level interventions as well. For example, the NHLBI-led Healthy Communities Study[509] examines 260 communities and almost 21,000 children, ages 3–15, to identify characteristics of existing obesity-related community programs and policies that are associated with less childhood obesity and better eating and physical activity behaviors. NHLBI also supports trials among American Indians and Alaska Natives to test community-responsive interventions to reduce childhood obesity and/or improve eating and activity behaviors in children.

Diseases such as obesity are more common in people with serious mental illness (SMI)—mental disorders resulting in significant functional impairment and illness, such as schizophrenia, bipolar disorder, and major depression—and lead to death 11–32 years earlier in these individuals compared to the general population.[510, 511] Modifiable risk factors—such as substance use, poor fitness, and diet—that contribute to these diseases are also more common and have an earlier onset in people with SMI. In 2013, NIMH-funded researchers reported that people with SMI could lose weight and keep it off through a modified lifestyle intervention program that involved bringing fitness instructors and nutritionists to places that people with SMI frequent.[512]

Finally, multiple efforts are underway to communicate evidence-based approaches toward preventing and treating obesity. Beginning in 2008, NHLBI supported a rigorous, evidence-based approach and innovative information technology to identify, review, and evaluate the scientific evidence for specific research questions to provide the basis for updated clinical obesity guidelines.[513] Public outreach efforts include *We Can!* (Ways to Enhance Children's Activity and Nutrition), a national public education outreach program to promote a healthy weight among children through efforts to improve food choices, increase physical activity, and reduce screen time. *We Can!* is managed by NHLBI with collaboration from NIDDK, NICHD, and NCI.

NIH collaborated with Home Box Office (HBO) on a documentary film series and public education campaign on obesity, entitled *The Weight of the Nation*, which was aired beginning in 2012. NIH staff provided scientific input to HBO on this project for several years. CDC and IOM also were involved, with IOM leading the coordination of government partners. The multipart documentary series included a four-part series of feature films, three films for youth and their families (HBO family series), and 12 supplemental films that were posted on the HBO website. Both the four-part feature films and the youth-focused films were nominated for Emmy Awards in 2012 and 2013. (The project was funded by HBO with support from Kaiser Permanente and the Michael & Susan Dell Foundation).[514]

Allergy and Asthma

Asthma

Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when you breathe), chest tightness, shortness of breath, and coughing and affects more than 25 million Americans, including nearly 7 million children age 17 and under.[515] Asthma is the leading cause of missed school days for children as well as preventable hospitalizations and emergency room visits. Blacks are disproportionately burdened by asthma, suffering at higher rates than do Whites and other minorities.[516] NIH supports targeted research to understand the causes of asthma and to develop preventions and treatments for the disease.

In late 2011, NHLBI launched the Consortium on Asthma among African-ancestry Populations in the Americas[517] to develop a customized "African power chip" to improve coverage and representation of all genes for increased power of GWAS in populations of African ancestry. This is complemented by genome sequencing studies to

[509] https://www.nhlbi.nih.gov/research/resources/obesity/population/hcs.htm.
[510] Colton CW, et al. *Prev Chronic Dis*. 2006;3(2):A42. PMID: 16539783.
[511] Druss BG, et al. *Med Care*. 2011;49(6):599–604. PMID: 21577183.
[512] http://www.nimh.nih.gov/news/science-news/2013/nih-study-shows-people-with-serious-mental-illnesses-can-lose-weight.shtml.
[513] http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/obesity-evidence-review/index.htm.
[514] http://www.nih.gov/health/NIHandweightofthenation/.
[515] http://www.nhlbi.nih.gov/health/health-topics/topics/asthma.
[516] http://www.cdc.gov/asthma/asthmadata.htm.
[517] http://www.caapaproject.net/index.php/home-top.

discover genes associated with asthma in African ancestry populations. These studies will help elucidate the genetics behind the racial disparity on asthma in this minority population, which suffers the highest burden of this disease.

NIAID's asthma research focuses on understanding how the environment, allergens, respiratory infections, and genetics interact with the body's immune system to cause asthma and aggravate its symptoms. The NIH Inner-City Asthma Consortium[518] ran Phase II studies from 2009 to 2014. The Consortium comprises 10 academic clinical centers and conducts large studies to evaluate the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. The Consortium also pursues observational studies to understand mechanisms underlying the onset and progression of asthma and research to develop diagnostic and prognostic biomarkers. One Consortium activity was to develop and validate a measure of asthma severity that takes into account symptoms, lung function, rate of asthma exacerbations, and medication requirements. This is the first tool of its kind, and it is expected to be used by many asthma clinical trials in the future.[519]

An NIEHS-supported study is testing whether using an Environmental Control System to remove allergens from indoor air, in addition to the use of medication, will provide a better solution for managing asthma among urban children, who have the highest asthma mortality rates in the U.S.

Allergy

An allergy is a reaction by the immune system to something that does not bother most other people. People who have allergies often are sensitive to more than one thing. Allergies can cause a variety of symptoms, such as a runny nose, sneezing, itching, rashes, swelling, or asthma, and the symptoms can range from minor to severe.

"Atopic" refers to a group of diseases in which there is often an inherited tendency to develop other allergic conditions, such as asthma and hay fever. Atopic dermatitis, or eczema, is a noncontagious, chronic inflammatory skin condition that affects an estimated 30 percent of the U.S. population, mostly children and adolescents. People with eczema also may be particularly susceptible to bacterial, viral, and fungal skin infections. NIAID supports both (1) basic studies on the immune mechanisms that contribute to atopic dermatitis and its complications and (2) patient-centered research that explores the genetic basis for the disease and evaluates new strategies for therapy and management. Among recent advances, intramural NIAID scientists showed that wet wrap therapy combined with education on long-term skin care can dramatically improve the lives of children with severe eczema.[520]

Food allergy affects between 4 and 6 percent of children and 4 percent of adults in the U.S., and its prevalence is increasing. NIAID is the lead Institute at NIH for research in food allergy and supports research to help better understand, prevent, and manage this disorder. Since 2003, NIAID has substantially increased its support for food allergy research, which now spans the spectrum from basic research to clinical trials that are testing new strategies to treat and prevent food allergy.

Significant advancement in the food allergy field was achieved by an NIAID-funded clinical trial showing that 75 percent of egg-allergic children can be helped to successfully tolerate egg by introducing it in small doses with increasing doses over time.[521] This approach, termed oral immunotherapy, is being tested with other foods and in combination with medications that may provide faster and more effective results.

Digestive Diseases

Digestive diseases span a wide spectrum of diseases and disorders that affect the GI tract, liver, gallbladder, and pancreas, many forms of which are chronic. Some digestive diseases are common, such as gastroesophageal reflux disease (GERD), whereas others are quite rare, such as genetic forms of liver disease. However, collectively they exact a significant toll on public health in terms of quality of life, years of life lost due to premature death, and costs

[518] http://www.niaid.nih.gov/topics/asthma/research/Pages/innerCity.aspx.
[519] Wildfire JJ, et al. *J Allergy Clin Immunol.* 2012;129(3):694–701. PMID: 22244599.
[520] http://www.niaid.nih.gov/topics/eczema/Pages/showcaseIntro.aspx.
[521] Burks AW, et al. *New Engl J Med*. 2012;367:233–43. PMID: 22808958.

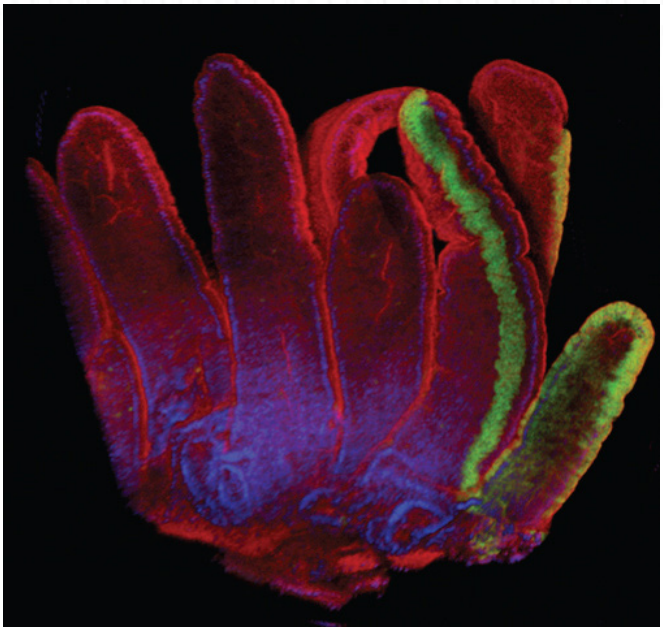


Figure 3-12. *Intestinal stem cells from a specific lineage (green) travel up finger-like projections called villi on the surface of the mouse intestine to replace cells that were lost following injury from radiation. This type of stem cell complements the functions of other types of stem cells present in the intestine, which are involved in repopulation during normal cell turnover. This image was captured using a technique called three-dimensional confocal reconstruction, which allows the visualization of gene expression. Credit: Manuel Amieva, M.D., Ph.D., Calvin Kuo, M.D., Ph.D., and Kelley Yan, M.D., Ph.D., Stanford University.*

associated with hospitalizations and pharmaceutical and surgical interventions. Additional information on some chronic digestive conditions and diseases is included in other sections of this report (e.g., IBS under "Chronic Pelvic Pain," IBD and celiac disease under "Autoimmune Diseases," cancers of digestive system under "Cancer," and viral hepatitis under "Infectious Diseases and Biodefense").

To reduce the public health burden of digestive diseases, NIH-supported scientists are vigorously pursuing research to better understand how widespread these diseases are across the U.S. and among specific populations; identify the causes of these diseases and how they progress; and test new interventions, including drugs, surgery, and behavior modification, for the prevention and treatment of these costly diseases. Major supporters of digestive diseases research at NIH include NIDDK as well as NCI and NIAID.

In addition to its extensive portfolio supporting individual investigators advancing digestive diseases research, NIDDK also supports multicenter research efforts, such as the Inflammatory Bowel Disease Genetics Consortium, Intestinal Stem Cell Consortium, Gastroparesis Clinical Research Consortium, Nonalcoholic Steatohepatitis Clinical Research Network, Childhood Liver Disease Research Network, Drug-Induced Liver Injury Network, adult and pediatric Acute Liver Failure Study Groups, and Hepatitis B Research Network, as well as 21 Digestive Diseases Research Centers located across the country. NIDDK also supports follow-up and ancillary studies to completed clinical trials in such areas as hepatitis C and adult-to-adult living donor liver transplantation.

Research suggests that bone marrow stromal cells (BMSCs) can travel to different parts of the body and work with immune cells to reduce inflammation and help repair damaged tissues. BMSC infusions have been used in promising experimental studies to treat moderate to severe IBD, but more research is needed. In 2013, NIAID investigators began a study at the NIH CC to further the understanding of the safety and effectiveness of BMSC infusions for the treatment of patients with moderate to severe Crohn's disease or ulcerative colitis who have not been helped by or cannot tolerate standard therapies.

Other recent advances point to new approaches for understanding, treating, and preventing these pervasive and debilitating disorders. A study conducted as part of NIDDK's Intestinal Stem Cell Consortium identified two distinct subpopulations of stem cells in the intestine—one that repopulates the tissue during normal cell turnover and another that replaces cells lost after injury.[522] NIDDK-sponsored scientists are gaining insights into the ways the microorganisms that inhabit the gut can tip the balance between digestive health and disease. For example, researchers have found that exposure to "friendly" microbes early in life can protect against inflammation in the gut.[523] Another study uncovered how a species of gut bacteria interacts with the immune system to suppress inflammation.[524] These studies in mice open the possibility

[522] Yan KS, et al. *Proc Natl Acad Sci*. 2012;109:466–71. PMID: 22190486.
[523] Olszak T, et al. *Science*. 2012;336:489–93. PMID: 22442383.
[524] Shen Y, et al. *Cell Host Microbe*. 2012;12:509–20. PMID: 22999859.

for future research in humans that could lead to new therapies for IBD. NIDDK also works closely with NHGRI in supporting research through the Human Microbiome Project, which is contributing to advancing understanding of digestive diseases and the role of microbial factors.

Research conducted through NIDDK's Nonalcoholic Steatohepatitis Clinical Research Network on nonalcoholic fatty liver disease, a common form of liver disease in U.S. adults and children, has shown benefits of vitamin E as a treatment for nonalcoholic steatohepatitis, or "NASH" (a type of fatty liver disease), in adults, as well as in children with the most severe form of the disease. NASH is the most rapidly growing reason for liver transplantation in the U.S. and, as the liver manifestation of the "metabolic syndrome," is increasing in frequency as a result of the increases in obesity and diabetes in the U.S. Recently, this Network has supported trials of additional new therapies in adults and children. In 2012, NIDDK entered into a cooperative research and development agreement (CRADA) with a pharmaceutical company to begin a clinical trial through the Network testing the safety and potential efficacy of a new treatment—cysteamine bitartrate—for NASH in children.[525] In other liver and biliary disease–related advances, scientists participating in the NIDDK's Childhood Liver Disease Research Network used patient samples and an animal model to identify a genetic deletion that may play a role in the development of biliary atresia, a life-threatening condition affecting newborns.[526]

NIDDK's Drug-induced Liver Injury Network collects and analyzes cases of severe liver injury caused by prescription and over-the-counter drugs as well as herbal products and supplements. The Network recently described the rising problem of liver injury from herbal medications and unregulated dietary supplements, which now accounts for 15–20 percent of cases, is often difficult to diagnose, and has a high fatality rate. In 2012, NIDDK, in conjunction with NLM, released "LiverTox," a website featuring sample cases of drug induced liver injury based on the Network data, as well as a database with summaries of liver injury reports for a given drug or herbal/dietary supplement.[527] The website serves as a public resource to aid health care providers in diagnosing, and investigators in studying, liver injury due to drugs and herbs/supplements. In 2013, NIDDK announced a new initiative to continue and expand the Network and the studies it enables.[528]

NIH, along with other federal and nonfederal partners, will continue efforts to address goals for advancing digestive diseases research as outlined in the NIH-led National Commission on Digestive Diseases research plan.[529] For example, NIDDK, together with NIAID, is continuing to support the Intestinal Stem Cell Consortium to stimulate basic research on the digestive system by developing new technologies to isolate, characterize, cultivate, and manipulate the system's stem cells.

Additionally, NIDDK is continuing support of its current research efforts in digestive diseases as well as pursuing new directions. For example, NIDDK is supporting new studies through the Hepatitis B Research Network to advance the understanding of the disease processes and inform effective treatment approaches. NIDDK hosted a workshop on *Developing a Clinical Research Agenda for Fecal Incontinence*, which focused on gaps in clinical and basic research for this condition, which affects nearly 18 million adults, as well as discussed recommendations to guide future research. In addition, NIDDK continues to manage a Bowel Control Awareness Campaign to help patient and health care professionals feel more comfortable talking about such conditions as fecal incontinence.[530] NIDDK also sponsored workshops to identify areas of new research opportunity related to pancreatitis, including one workshop in June 2012 on the NIH campus in Bethesda, MD., on *Advances in Acute and Chronic Pancreatitis: From Development to Inflammation and Repair* and another in June 2013 on the NIH campus, co-sponsored with NCI, on *Pancreatitis, Diabetes, Pancreatic Cancer*.

Kidney Diseases

Normal, healthy kidneys filter about 200 quarts of blood each day, generating about two quarts of excess fluid, salts, and waste products that are excreted as urine. Loss

[525] http://www.nih.gov/news/health/jan2012/niddk-11.htm.
[526] Cui S, et al. *Gastroenterology*. 2013;144:1107–15. PMID: 23336978.
[527] http://livertox.nih.gov/.
[528] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-502.html.
[529] http://www.niddk.nih.gov/about-niddk/strategic-plans-reports/Pages/opportunities-challenges-digestive-diseases-research-recommendations-national-commission-digestive-disease.aspx.
[530] http://www.bowelcontrol.nih.gov/.

of function of these organs, due to a variety of causes, can result in life-threatening complications. For example, in people with polycystic kidney disease, fluid-filled cysts form in the kidneys and other organs and can, as they grow over time, compromise kidney function. There is no treatment that can restore kidney function once it has been lost; patients require either dialysis or a transplant to survive.

Led by NIDDK, NIH has robust basic, clinical, and translational research portfolios targeting kidney diseases. Research on kidney development and disease includes research on the causes of kidney disease, the biology of normal kidney function, and the underlying mechanisms leading to the progression of kidney disease and end-stage renal disease that results in the need to replace kidney function through dialysis or transplantation. NIH research also focuses on the identification and testing of possible treatments to prevent the development or halt the progression of kidney disease. NIDDK also supports studies of inherited kidney diseases, such as polycystic kidney disease, congenital kidney disorders, and immune-related kidney diseases, including IgA nephropathy and hemolytic uremic syndrome.

NIDDK-supported clinical trials are exploring new treatment options and identifying novel links between kidney disease and its many comorbid conditions, including CVD. For example, the Chronic Renal Insufficiency Cohort Study,[531] co-sponsored by NIDDK and NHLBI, is evaluating long-term cardiovascular risk and outcomes of over 3,700 persons with CKD. This study is part of a broader effort by NIH to identify biomarkers that can allow physicians to better predict how various diseases are likely to progress in different patients and thereby personalize treatments to improve their health.[532]

The Chronic Kidney Disease in Children Cohort Study[533] is following more than 500 children with mild to moderately decreased kidney function in order to identify risk factors for further decrease in kidney function; monitor brain development; examine risk factors for heart disease; and look at the long-term effects of poor growth in this group. The study has shown that, in children with CKD, complications occur early, suggesting the need for earlier, more aggressive management of blood pressure, anemia, and other problems.[534] Additionally, this study found that these children were less likely to grow to normal height ranges if they came from lower-income families.[535]

NIA collaborates with NIDDK to support research on renal function and CKD in aging. Projects include basic, clinical, and translational research on CKD and its consequences in aging and in older persons, focusing on biology and pathophysiology of CKD in animal models; etiology and pathophysiology of CKD in the elderly; epidemiology and risk factors for the development of CKD with advancing age; and/or diagnosis, medical management, and clinical outcomes of CKD in this population.[536, 537]

In order to identify and validate biomarkers, which should stimulate bench to bedside translation and may enhance researchers' ability to evaluate promising new therapies in clinical trials, NIDDK supports the Chronic Kidney Disease Biomarkers Consortium.[538] NIDDK also is studying acute kidney injury (also called acute renal failure), which is a relatively common complication in hospitalized patients. The Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury, a study of the natural history of patients with acute kidney injury, will provide important information about the natural history of acute kidney injury and recovery.[539]

NIAID, along with NHLBI and NIDDK, supports the Clinical Trials in Organ Transplantation program,[540] which aims to enhance the understanding, and ultimately reduce the immune-mediated morbidity and mortality, of organ transplantation, including kidney transplantation. NIAID and NHLBI also fund the Clinical Trials in Organ Transplantation in Children,[541] which aims to improve short- and long-term graft and patient survival in children who have undergone heart, lung, and kidney transplantation. The Immune Tolerance Network,[542] a clinical research consortium

[531] http://cristudy.org/Chronic-Kidney-Disease/Chronic-Renal-Insufficiency-Cohort-Study/.
[532] https://www.clinicaltrials.gov/ct2/show/NCT00327860.
[533] http://statepi.jhsph.edu/ckid/.
[534] Furth SL, et al. *Clin J Am Soc Nephrol*. 2011;6:2132–40. PMID 21841064.
[535] Hidalgo G, et al. *Am J Kidney Dis*. 2013;62(6):1087–94. PMID 23932090.
[536] http://grants.nih.gov/grants/guide/pa-files/PA-09-165.html.
[537] http://grants.nih.gov/grants/guide/pa-files/PA-09-166.html.
[538] http://www.ckdbiomarkersconsortium.org/.
[539] http://medicine.yale.edu/intmed/patr/projects/assess-aki.aspx#page1.
[540] https://www.ctotstudies.org/.
[541] https://www.ctotc.org/.
[542] http://www.immunetolerance.org/.

sponsored by NIAID, is dedicated to the clinical evaluation of novel therapies that are designed to promote immune system tolerance in autoimmune and allergic diseases and, therefore, prevent rejection of transplanted tissues, cells, and organs (including kidney).

NCI and NIDDK researchers are collaborating in research regarding focal segmental glomerulosclerosis, the leading cause of primary nephrotic syndrome in adults and the leading cause of end-stage renal disease in children, as well as HIV-associated nephropathy, a disorder that occurs in 10 percent of untreated HIV-infected persons of African descent, but is rarely observed in non-Africans. Previous studies have found that African-Americans with two variants of the *APOL1* gene have about a 4 percent lifetime risk of developing focal segmental glomerulosclerosis. These findings explain nearly all of the excess risk of nondiabetic kidney failure in African Americans. *APOL1* gene variants have been found to be associated with the rate of decline in kidney function in African Americans[543] as well as with the age at which individuals begin hemodialysis to treat kidney failure.[544] NIH also is supporting research into glomerular diseases through the Cure GN Network and NEPTUNE study, which seek to expand researchers' and physicians' knowledge about several forms of glomerular disease.

Urologic Diseases and Conditions

Diseases and conditions affecting the bladder and associated structures of the lower urinary tract affect people of all ages, result in significant health care expenditures, and may lead to substantial disability and impaired quality of life.

Spearheaded by NIDDK, NIH supports basic and clinical research on the normal and abnormal development, structure, function, and injury repair of the genitourinary tract. Areas of particular interest include the causes of and treatments for major adult urological diseases and disorders, such as benign prostatic hyperplasia (BPH), urinary incontinence (UI) and urinary tract infections (UTIs). (Other disorders of the genitourinary tract, such as interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome, are discussed under "Chronic Pelvic Pain," in this subsection). Additional areas of interest include research on treatments for kidney stones (hard masses developed from crystals that separate from the urine within the urinary tract), such as shock-wave and laser lithotripsy to break up stones, and therapeutic approaches to inhibit their formation and growth.

Based on national public health surveys conducted over several years, it is estimated that 1 in 10 U.S. adults (18 years and older) suffer from daily UI, making this a widespread health issue for many people in the U.S.[545] Similarly, UTIs are among the most common infectious diseases acquired by humans; in fact, only respiratory infections occur more often. UTIs caused by the bacterium *Escherichia coli (E. coli)*, which is normally found in the colon, accounted for over 6.6 million doctor visits, nearly 5.4 million by women in 2007, and many women suffer from frequent infections.[546] Women are disproportionately affected by many urologic diseases and conditions, such as UI, UTIs, and IC/PBS.[547] NIH places particular emphasis on preventing urologic problems in women, including promoting the development of alternatives to antibiotic treatment for UTIs and finding new ways to prevent or treat UI.

With co-funding from ORWH, the NIDDK-supported Urinary Incontinence Treatment Network investigated surgical, behavioral, and medical treatments for stress and urge UI. One of the network's studies revealed that invasive and costly tests commonly performed in women before surgery for stress urinary incontinence (SUI) may not be necessary in many cases.[548] A two-year follow-up study to the Trial of Mid-Urethral Slings, a clinical trial that compared the outcomes of two minimally invasive surgical procedures involving use of FDA-approved synthetic mesh slings to treat SUI in women, suggests that women who have had this type of surgery would benefit from continued monitoring for complications post-surgery.[549] Having the information from these studies will better equip women with SUI and their doctors in planning a course of treatment. Discovery research in animal models also is revealing clues to bladder control. For example, results from a study in mice suggest

[543] Lipkowitz MS, et al. *Kidney Int*. 2013;83(1):114–20. PMID 22832513.
[544] Kanji Z, et al. *J Am Soc Nephrol*. 2011;22(11):2091–7. PMID 21997398.
[545] http://udaonline.net/pdf-compendium/v2012.
[546] http://kidney.niddk.nih.gov/statistics/uda/Urologic_Diseases_in_America.pdf.
[547] http://udaonline.net/pdf-compendium/v2012.
[548] Nager CW, et al. *N Engl J Med*. 2012;366(21):1987–97. PMID: 22551104.
[549] Albo ME, et al. *J Urol*. 2012;188(6):2281–87. PMID: 23083653.

that in addition to bladder nerves and muscle, cells lining the bladder play a role in transmitting mechanosensory signals about the bladder's shape and level of fullness that are important to appropriate bladder control—results that can now be investigated for their relevance to human urologic conditions.[550]

NIDDK and other ICs support basic and clinical research on UTIs to elucidate the cause(s) and illuminate potential treatment approaches for acute and recurrent UTIs. For example, scientists at a Specialized Center of Research on Sex Differences, co-supported by NIDDK and ORWH, have made tremendous progress in understanding factors in both the host organism (e.g., human, mouse) and the infecting bacteria that contribute to the onset and recurrence of UTIs. Based on knowledge gained through these studies, researchers have identified novel orally active compounds that in mouse models of infection, appear to block bacteria from binding to bladder cells, thereby preventing new UTIs and mitigating chronic infections. This promising finding of an alternative to antibiotic treatment for UTIs can now be further pursued to develop more potent compounds and assess them for toxicity before testing them in humans.[551]

NIH's focus on improving men's urologic health includes finding new ways to treat BPH and other diseases of the prostate. Noncancerous growth of the prostate, or BPH, is a common cause of bothersome lower urinary tract symptoms, such as weak or intermittent urine stream, an inability to empty the bladder completely, and having to urinate frequently, especially at night. The prevalence of BPH increases from 40 to 50 percent in men ages 51– 60 to greater than 80 percent in men older than 80.[552] Congenital malformations or obstructions of the urinary tract can lead to a variety of urologic problems in children, including reflux of urine back toward the kidneys (vesicoureteral reflux) and UTIs. Urologic diseases and disorders also can contribute to or be the primary cause of sexual dysfunction. As people age, many noncancerous urologic conditions become more prevalent. Thus, addressing the burden of urologic diseases and conditions is an important challenge to meet as the American population ages overall.

An NIDDK-supported study using patient data from men enrolled in the Prostate Cancer Prevention Trial found that men who had received the drug finasteride, which has been shown to be effective in relieving the symptoms of BPH, had a 40 percent lower chance of developing BPH than men who did not receive the drug. These results suggest that finasteride may be an effective preventative therapy in men without overt symptoms of BPH.[553]

Other initiatives include the GenitoUrinary Development Molecular Anatomy Project,[554] a NIDDK-funded consortium of laboratories working to provide the scientific and medical community with tools to facilitate research on the genitourinary tract. Another NIDDK-supported effort, the 2012 Urologic Diseases in America,[555] incorporates current and retrospective data on all aspects of the epidemiology, practice patterns, costs, and impact of urologic diseases in the U.S., and is intended for use by public officials, nongovernment organizations, the media, academic researchers, health professionals, and the public.

Diabetes

NIH continues to be guided by Advances and Emerging Opportunities in *Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee*,[556] published in February 2011, which identifies compelling opportunities for research over the next decade on diabetes and its complications.

Type 1 Diabetes

Type 1 diabetes is an autoimmune disease that often strikes during infancy, childhood, or young adulthood, but, although the incidence of type 1 diabetes is increasing, people with type 1 diabetes are living longer, healthier lives than ever before. NIDDK's landmark Diabetes Control and Complications Trial, conducted from 1983 to 1993, showed that intensive glucose control dramatically delays or prevents eye, nerve, and kidney complications of type 1

[550] Kanasaki K, et al. *FASEB*. 2013;27(5):1950–61. PMID: 23395910.
[551] Cusumano CK, et al. *Sci Transl Med*. 2011; 3(109):109ra115. PMID: 22089451.
[552] http://www.niddk.nih.gov/health-information/health-topics/urologic-disease/benign-prostatic-hyperplasia-bph/Pages/facts.aspx.
[553] Parsons JK, et al. *Eur Urol*. 2012;62(2);234–41. PMID: 22459892.
[554] https://www.gudmap.org/.
[555] http://udaonline.net/pdf-compendium/v2012.
[556] http://www.niddk.nih.gov/about-niddk/strategic-plans-reports/Documents/2011-02_Advances%20and%20Emerging%20Opportunities%20in%20Diabetes%20Research_A%20Strategic%20Planning%20Report%20of%20the%20Diabetes%20Mellitus%20Inte/DSP2011_FullDocument_508%5b1%5d.pdf.

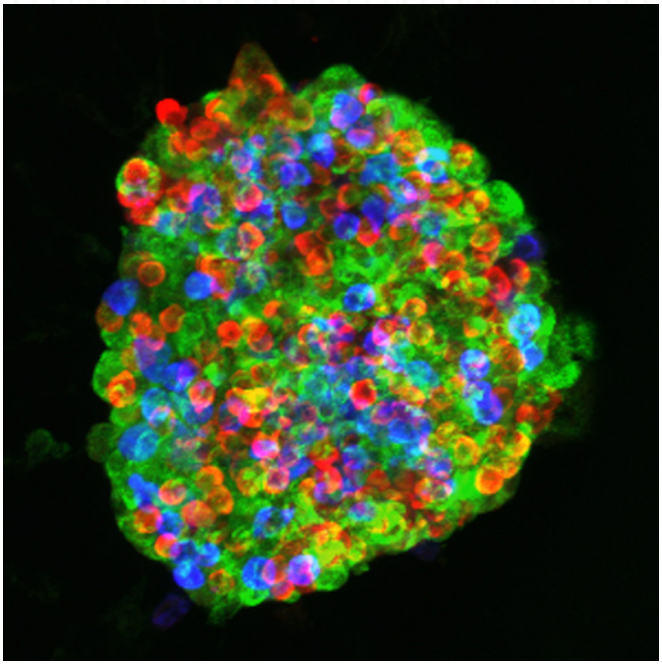


Figure 3-13. *A human pancreatic islet, which contains many different cell types, including insulin-producing beta (ß) cells (stained green) and glucagon-producing alpha cells (stained red). Credit: Alvin Powers, M.D., and Marcela Brissova, Ph.D., Vanderbilt University.*

diabetes.[557] A paradigm shift in the way type 1 diabetes is controlled was based on this finding. The follow-on study, Epidemiology of Diabetes Interventions and Complications Study, showed that tight glucose control also prevents or delays the cardiovascular complications of type 1 diabetes, lowers the occurrence of vision-threatening diabetic eye disease or need for eye surgery, and preserves kidney function for decades. This finding shows that the benefits of early and intensive therapy can persist for decades. It also demonstrates the importance of long-term research, when the full benefit of treatment may not be seen for long time periods.

Because of treatment improvements and new technologies, the long-term survival of those with type 1 diabetes has improved dramatically during the past 30 years. However, disease management to reduce risk for complications places an enormous burden on patients. Thus, it is imperative to pursue research on new methods, such as artificial pancreas technology, to improve type 1 diabetes control and reduce the burden on patients. Artificial pancreas technology—in which a continuous blood glucose sensor is linked to a computer that calculates the amount of insulin needed in response to the blood glucose level and an insulin delivery system—has high potential to have a positive impact on patients' health and quality of life. Major efforts to address type 1 diabetes—particularly focused on diabetes complications and beta cell research as well as hemoglobin A1c standardization—are also of great importance for reducing the burden of type 2 diabetes.

The incidence of type 1 diabetes is increasing at 3 percent per year, suggesting that one or more unknown environmental factors are involved in triggering the disease. Type 1 diabetes is one of the few polygenic diseases for which more than 70 percent of the genetic basis of the disease has been identified. With the identification of additional risk genes and biomarkers, it is now possible to predict risk of developing type 1 diabetes. This ability has enabled the launch of prevention studies as well as studies to identify environmental trigger(s).

Current research on type 1 diabetes supports the following broad goals: (1) identify the genetic and environmental causes; (2) prevent or reverse the disease; (3) develop cell replacement therapy; (4) improve type 1 diabetes management and care (including development of artificial pancreas technologies); and (5) prevent or reduce the complications of the disease. Type 1 diabetes research at NIH is supported by regular appropriations and by the Special Statutory Funding Program for Type 1 Diabetes Research, a program administered by NIDDK on behalf of the HHS Secretary and in collaboration with other NIH ICs.

Major research efforts include Type 1 Diabetes TrialNet, an NIDDK-led international clinical trials network that screens large numbers of individuals and conducts trials of agents to prevent type 1 diabetes in at-risk people and slow progression of the disease in people who are newly diagnosed. Blood tests can accurately identify relatives of people with type 1 diabetes who are at high or moderate risk of developing the disease within five years. This has enabled TrialNet to launch clinical trials of promising prevention strategies, three of which (oral insulin, abatacept, and teplizumab) are currently ongoing.[558] Both abatacept and teplizumab showed short-term efficacy in preserving insulin secretion in people recently diagnosed with type 1 diabetes,

[557] http://diabetes.niddk.nih.gov/dm/pubs/control/.

[558] http://www.diabetestrialnet.org/.

and now these treatments are being tested to determine whether they can delay or prevent disease in people at risk for, but not yet diagnosed with, type 1 diabetes.

Other NIDDK studies aim to develop new ways to predict and treat type 1 diabetes complications. NIDDK's Preventing Early Renal Function Loss in Diabetes clinical trial is examining whether the drug allopurinol—currently used for treating gout—could preserve kidney function in people with type 1 diabetes who are at high risk of kidney disease. The trial has the potential to identify an inexpensive approach to preserving kidney function in people with type 1 diabetes.

The Environmental Determinants of Diabetes in the Young (TEDDY) is an NIDDK-led study to identify the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. The TEDDY study has completed enrollment of more than 8,000 high-risk newborns and is collecting biosamples and data for analysis to identify potential triggers of type 1 diabetes. TEDDY researchers determined that diabetic ketoacidosis, a potentially life-threatening condition, occurred less frequently in TEDDY participants with type 1 diabetes than in those with type 1 diabetes who did not take part in TEDDY, suggesting that increased screening and monitoring may reduce the occurrence of diabetic ketoacidosis in children with type 1 diabetes.[559] TEDDY investigators are beginning other pilot studies to identify biomarkers predictive of autoimmunity and type 1 diabetes. NIAID, NIEHS, and NICHD also participate in the TEDDY study.

Two groups of scientists in NIDDK's Beta Cell Biology Consortium—a consortium of researchers studying pancreatic islets and beta cell biology and development toward a cell-based treatment for diabetes—discovered that the adenosine signaling pathway is a key regulator of beta cell regeneration and demonstrated that compounds that target this pathway increased beta cell proliferation in various nonhuman models.[560, 561] In addition, other researchers discovered the hormone betatrophin, which triggered proliferation of beta cells in mice and led to increased beta cell mass and improved glucose tolerance.[562] Collectively, this research could inform new strategies to promote beta cell regeneration and function.

Data reported by NIDDK's Collaborative Islet Transplant Registry suggest that islet transplantation is improving and continues to be a promising avenue for treating people with difficult-to-manage type 1 diabetes. The data showed that the percentage of people who did not need external insulin administration three years after their islet transplant increased over time—from 27 percent to 37 percent to 44 percent in 1999–2002, 2003–2006, and 2007–2010, respectively. The transplanted islets also functioned longer in the most recent period, and the procedure protected patients from severe episodes of hypoglycemia.[563] Many of the recent transplants were performed by the Clinical Islet Transplantation Consortium (CIT), which is co-led by NIDDK and NIAID. The Consortium is conducting clinical and mechanistic studies in islet transplantation, with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. The Consortium has completed enrollment of a pivotal (Phase III) islet transplantation trial (islet transplant alone). The trial has reached its primary endpoint, and its results are intended to support future FDA licensure of an islet product.

To overcome the limitations of current insulin therapy, researchers have long sought to link glucose monitoring and insulin delivery by developing artificial pancreas technology. Tremendous progress has been made toward the development of artificial pancreas technology that will mimic as closely as possible the way a healthy pancreas detects changes in blood glucose levels and responds automatically to secrete appropriate amounts of insulin. All of the current continuous glucose monitoring technology on the market benefitted from NIDDK support early in development. NICHD and NIBIB have joined NIDDK in supporting small-business initiatives aimed at further development of these and related technologies. Clinical studies on closed-loop technologies are now ongoing, including trials testing these technologies in adults and adolescents in real-world settings and trials testing unsupervised nighttime use of closed-loop systems. NIDDK also is supporting research training of engineers and behavioral scientists—those in fields that are critical for propelling progress in this area.

[559] Elding Larsson H, et al. *Diabetes Care*. 2011;34:2347–52. PMID: 21972409.
[560] Andersson O, et al. *Cell Metab*. 2012;15:885–94. PMID: 22608007.
[561] Annes JP, et al. *Proc Natl Acad Sci U S A*. 2012;109:3915–20. PMID: 22345561.
[562] Yi P, et al. *Cell*. 2013;153:747–758. PMID: 23623304.
[563] Baron FB, et al. *Diabetes Care*. 2012;35:1436–45. PMID: 22723582.

Figure 3-14. *The Diabetes Research in Children Network, led by NICHD, is a research consortium investigating hypoglycemia and use of continuous glucose monitoring in children. Credit: istockphoto.com.*

One example of an advance in artificial pancreas technology is the use of smartphone technology to control a closed-loop artificial pancreas system. Previously, closed-loop systems had been tested in people in hospital settings using laptop computers, but the laptops limited mobility. Toward the goal of developing a portable, usable, and safe artificial pancreas system, scientists developed and tested the ability of a smartphone technology called the Diabetes Assistant to replace a laptop in this system. Closely monitored participants used the system on their own, stayed in real-world settings, and ate whatever they wanted. The study found that the artificial pancreas system had proper system communication 98 percent of the time, demonstrating that smartphone technology could be used to run a closed-loop system.[564] Other NIDDK-supported studies testing smartphone-based technologies are now ongoing with promising early results.

NICHD supports a diverse research portfolio related to type 1 diabetes in children and in pregnant women, including research on the risk of pregnancy complications for women with type 1 diabetes, metabolic processes underlying the severity of type 1 diabetes in children, and behavioral research on the maintenance of glycemic control in children and adolescents, as well as in other scientific

[564] Kovatchev BP, et al. *Diabetes Care*. 2013;36:1851–8. PMID: 23801798.

areas. For example, NICHD leads the Diabetes Research in Children Network,[565] a research consortium investigating hypoglycemia and use of continuous glucose monitoring in children, as well as the Trial to Reduce the Incidence of Type 1 Diabetes for those Genetically at Risk clinical trial. This trial examines whether hydrolyzed infant formula, compared to standard cow's milk-based formula, decreases the risk of developing type 1 diabetes in a large cohort of more than 2,000 children who are at high genetic risk for this disorder.[566]

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is an NEI-led, collaborative, nationwide network of eye doctors and investigators conducting multicenter clinical trials of diabetes-induced eye disease, including comparative effectiveness research on new therapies. By providing infrastructure for conducting multiple concurrent studies, DRCR.net enables rapid development, initiation, and patient recruitment for new protocols and provides opportunities for industry collaborations while maintaining a rigorous academic environment.

The National Glycohemoglobin Standardization Program, supported by NIDDK, is achieving international standardization and reliability in measuring HbA1C, a blood test that measures glycosylated hemoglobin and is a good surrogate measure of long-term blood glucose control and, as such, reflects risk of diabetic complications.[567]

Research will build on the unprecedented recent discoveries of genes and gene regions contributing to type 1 diabetes to understand their function in health and disease. This research could illuminate new targets for therapy. Research will also develop, refine, and pilot test innovative strategies to improve adherence to medications and medical regimens in children, adolescents, and young adults with type 1 diabetes and also seek to understand barriers and facilitators to type 1 diabetes management in adults.

Type 2 Diabetes

In type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. At first, the pancreas produces more insulin to compensate. Gradually, however, blood glucose levels rise as the pancreatic beta cells lose their capacity to secrete insulin, and the timing of insulin secretion becomes abnormal. Treatment approaches for controlling glucose levels include diet, exercise, and oral and injected medications; insulin often is required as the disease progresses. Risk factors include being overweight, age, racial or ethnic background, history of gestational diabetes, and family history of type 2 diabetes.

NIH supports research to better understand metabolism and the mechanisms that lead to the development and progression of diabetes; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, NIH is vigorously pursuing studies of prevention and treatment approaches. Research on type 2 diabetes and its complications is spearheaded by NIDDK, with complementary efforts and collaborations with many other NIH ICs and Offices, including NHLBI, NEI, NINR, NIEHS, NINDS, NIA, and ORWH.

Critical programs in type 2 diabetes include a new NIDDK-led consortium, Optimizing Recovery and Preservation of Endogenous Insulin Secretion, that explores approaches to slow beta cell loss in prediabetes and early type 2 diabetes.[568] Another NIDDK-led consortium, the Multiethnic Study of Type 2 Diabetes Genes Consortium, has been working to define genes or gene regions conferring type 2 diabetes risk in multiple ethnic groups.[569] Results from these efforts, as well as many other NIDDK-led genetic studies of type 2 diabetes, are now informing the new Accelerating Medicines Partnership Type 2 Diabetes Project, a collaboration of NIH, 10 biopharmaceutical companies, FDA, and several nonprofit organizations. The Partnership plans to leverage the wealth of new data on type 2 diabetes genetics, supplementing it as necessary, to identify and validate novel molecules and pathways as targets for therapeutic development.

NIDDK's Translational Research for the Prevention and Control of Diabetes and Obesity[570] and NIDDK Centers for Diabetes Translation Research fund type 2 diabetes

[565] https://www.nichd.nih.gov/research/supported/Pages/directnet.aspx.
[566] https://www.nichd.nih.gov/research/supported/Pages/TRIGR.aspx.
[567] http://www.ngsp.org/index.asp.
[568] http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-10-013.html.
[569] http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-004.html.
[570] http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html.

translational research (e.g., bedside to practice and the community) based on past successful diabetes clinical trials. Among the projects funded by these programs will be those that lower the cost and increase the availability of lifestyle interventions to prevent diabetes based on the intervention found highly effective in NIDDK's landmark Diabetes Prevention Program clinical trial.[571]

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study is a major NIDDK-supported trial launched in 2013 that compares common diabetes medications to determine which drug—in combination with the safe and well-tolerated drug metformin—is most safe and effective for patients. The study will recruit 5,000 participants diagnosed with type 2 diabetes within the last 10 years at more than 30 clinical sites around the country and will include broad representation of racial and ethnic groups at elevated risk for type 2 diabetes.

Look AHEAD (Action for Health in Diabetes) is another major NIH clinical trial in people with type 2 diabetes that is funded by NIDDK and other NIH ICs. Look AHEAD was designed to determine whether an intensive lifestyle intervention designed to promote weight loss through decreased caloric intake and increased physical activity can improve health outcomes in people who have obesity and type 2 diabetes. After nearly 10 years of follow-up, the numbers of CVD events did not differ significantly between the intensive lifestyle intervention group and the diabetes support and education group. However, this intervention did lead to weight loss and better maintenance of weight loss as well as improved fitness, glucose control, and blood pressure, with less use of medication. Other health benefits of the intervention included partial remission of the diabetes, a slower decline in mobility, and reduced sleep apnea.[572, 573, 574, 575]

NIDDK also leads the Diabetes Prevention Program (DPP) Outcomes Study with additional support from NHLBI, ORWH, NIA, NICHD, and NEI. The DPP Outcomes Study[576] is following participants in the landmark DPP to determine long-term outcomes and durability of DPP interventions. The DPP Outcomes Study has found that the metformin and lifestyle interventions continue to be effective for at least 10 years; the DPP lifestyle intervention is especially effective in people older than age 60 and is highly cost-effective; the metformin intervention is about as effective as the lifestyle intervention in women with a history of gestational diabetes and in people younger than age 45, but is much less effective than the lifestyle intervention in older participants; and metformin is not merely cost-effective, but is actually cost-saving. The study also has made numerous other important findings, including the pharmacogenomic characterization of a gene influencing the transport and effectiveness of metformin, currently the most important medication in the treatment of type 2 diabetes. In addition, the study is examining intervention effects on other health-related outcomes, including comorbid conditions such as depression.

The NIDDK Treatment Options for Type 2 Diabetes in Adolescents and Youth trial demonstrated how difficult it is to treat type 2 diabetes in children. Analyses of trial data now show that average insulin-production capacity fell among all groups; insulin-sensitivity, though initially boosted among participants taking rosiglitazone, subsequently fell in all groups.[577] Participants were also found to have alarming early signs of retinopathy,[578] kidney disease,[579] and cardiovascular risk factors.[580] Poor metabolic control and likelihood of complications were associated with greater time from type 2 diabetes onset to initiation of treatment, highlighting the urgency of earlier intervention as well as prevention and improved treatment.

NHLBI leads a nontreatment observational follow-up study titled ACCORDION of more than 8,000 participants who took part in the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[581] clinical trial in people with type 2 diabetes who were at high risk of CVD. ACCORD tested the effects of three different treatment strategies for controlling glucose, blood pressure, or lipids, respectively, on the rate of CVD events (i.e., heart attack, stroke, death) and

[571] http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-10-009.html.
[572] Look AHEAD Research Group, et al. *N Engl J Med*. 2013;369(2):145–54. PMID: 23796131.
[573] Gregg EW, et al. *JAMA*. 2012;308:2489–96. PMID: 23288372.
[574] Rejeski WJ, et al. *N Engl J Med*. 2012;366:1209–17. PMID: 22455415.
[575] Kuna ST, et al. *SLEEP*. 2013;36:641–9. PMID: 23633746.
[576] http://www.niddk.nih.gov/news/for-reporters/diabetes-prevention-program-outcomes-study/Pages/default.aspx.
[577] TODAY Study Group. *Diabetes Care*. 2013;36(6):1749–57. PMID: 23704674.
[578] TODAY Study Group. *Diabetes Care*. 2013;36(6):1772–4. PMID: 23704677.
[579] TODAY Study Group. *Diabetes Care*. 2013;36(6):1735–41. PMID: 23704672.
[580] TODAY Study Group. *Diabetes Care*. 2013;36(6):1758–64. PMID: 23704675.
[581] http://www.accordtrial.org.

followed participants for approximately five years. The study showed that intensive blood pressure[582] and combination lipid[583] therapies did not reduce CVD events and, compared with the standard glucose treatment strategies, intensive treatment resulted in higher mortality. ACCORDION followed ACCORD participants from 2011 to 2014 to elucidate the long-term effects of ACCORD interventions and provide additional data on the long-term relationships among various cardiovascular and diabetic risk factors.

The landmark diabetic macular edema (DME) trial[584] demonstrated that eye injections of vascular endothelial growth factor (VEGF)–inhibitor Lucentis, along with prompt or deferred laser treatment, were superior to the standard therapy of laser alone. Building on these findings, the NEI-funded Diabetic Retinopathy Clinical Research Network launched a comparative effectiveness trial of Lucentis, Avastin, and EYLEA for DME. Although these drugs are similar and act on the same molecular pathway, they differ in cost and treatment duration. This DME trial, which started in 2013 and ended in 2014, was developed to clarify treatment options for patients and clinicians. First year results from the trial showed that all three drugs were safe and effective at improving vision in diabetic retinopathy. All three drugs performed similarly when patients' initial vision loss was mild. However, patients who started the trial with worse baseline vision manifested greater improvement with Eylea than with the other two drugs. These results reinforce that patients have multiple treatment options based on their personal needs and should discuss their treatment options with their doctors.[585]

Other significant research efforts include the NIEHS National Toxicology program (NTP),[586] in which researchers are examining how to incorporate information on nuclear receptor signaling and stress pathways into the Tox21 framework for chemical screening. These efforts create an opportunity to use Tox21 approaches to identify substances of concern, exposure to which may increase diabetes risk. NIEHS, NICHD, and NIDDK co-fund the Role of Environmental Chemical Exposures in the Development of Obesity, type 2 Diabetes and Metabolic Syndrome research program to investigate links between environmental exposure and the increased incidence of weight gain, glucose tolerance/insulin sensitivity, and aspects of metabolic syndrome in animal models or human studies.

NIMH is supporting a randomized control trial on a psychosocial intervention for people with serious mental illness and comorbid diabetes. Patients meet in groups with nurses and peers who have been trained in illness self-management to drive positive behavior change and active self-management to address both the mental disorder and diabetes in an integrated fashion.

NIDDK-supported research advances include further understanding of both the mechanisms underlying diabetes and the modes of action of some of the current interventions. For example, the type 2 diabetes drug metformin has been shown to limit hepatic glucose production by inhibiting adenylate cyclase, the primary step in signal transduction from glucagon,[587] and beta cell–specific long noncoding RNAs appear to regulate transcription in islets and to express abnormally in type 2 diabetes.[588]

Substance Abuse and Addiction

Nearly four decades of NIH-supported research have proven that substance addiction is a complex brain disease characterized by compulsive, and at times uncontrollable, drug or alcohol craving, seeking, and use that persists despite potentially devastating consequences. Once addiction takes hold in the brain, it disrupts a person's ability to exert control over his or her behavior, reflecting the compulsive nature of this disease. In fact, many of the substance-induced brain adaptations can be long lasting, which is, in part, why addiction is considered a chronic disease. Similar to the more classic chronic diseases (e.g., diabetes, hypertension, heart disease), most addicted patients require long-term treatment, and relapse (re-emergence of symptoms) may occur during the treatment or recovery process.[589]

[582] ACCORD Study Group, et al. *N Engl J Med*. 2010;362(17):1575–85. PMID: 20228401.
[583] ACCORD Study Group, et al. *N Engl J Med*. 2010;362(17):1563–74. PMID: 20228404.
[584] Elman MJ, et al. *Ophthalmology*. 2011;118(4):609–14. PMID: 21459214.
[585] Diabetic Retinopathy Clinical Research Network, et al. *N Engl J Med*. 2015;372(13):1193–203. PMID: 25692915.
[586] http://ntp.niehs.nih.gov/.
[587] Miller RA, et al. *Nature*. 2013;494(7436):256–60. PMID: 23292513.
[588] Moran I, et al. *Cell Metab*. 2012;16(4):435–8. PMID: 23040067.
[589] http://www.drugabuse.gov/publications/science-addiction.

NIDA's and NIAAA's diverse research portfolios for FY 2012–2013, reflected in their strategic plans,[590, 591] are geared toward addressing substance use, substance misuse, and the escalation of substance use to addiction; developing successful treatments for substance use disorders (SUD); and improving treatment accessibility and implementation. Integrating NIDA's and NIAAA's intramural clinical programs will undoubtedly enhance these efforts toward translating basic and preclinical data into therapeutic strategies for underserved patient populations. NCI also supports research in this area, particularly with regard to smoking cessation and tobacco control. In addition, research on the cycle of substance misuse naturally extends to the critical research needed to address the medical (e.g., HIV, liver disease, fetal alcohol spectrum disorders (FASDs), social, and legal consequences of SUD. NIH established the Collaborative Research on Addiction at NIH initiative,[592] which provides a framework for NIAAA, NIDA, and NCI to integrate resources and expertise to promote and enhance collaborative research in substance use, misuse, addiction, and the related consequences. This program focuses on cross-cutting areas in addiction research to provide new insight into understanding and addressing specific SUD and co-occuring SUD (e.g., dependence on both alcohol and drugs) as well as co-occurring behavioral health problems. Research areas on the prevention of substance misuse and addiction include genetics, development, and basic neurobiology as well as behavioral, social, and policy-related strategies to prevent and intervene with substance use initiation and the transition to addiction. Large-scale epidemiological studies, such as NIDA's Monitoring the Future survey of 8th, 10th, and 12th graders and NIAAA's National Epidemiologic Survey on Alcohol and Related Conditions of adults age 18 and older, provide information on substance use and misuse as well as co-occurring conditions that can inform and target prevention and treatment efforts.

Basic Research on Substance Abuse and Addiction

NIDA and NIAAA continue to support basic research on the etiology and biological underpinnings of addiction to advance scientific knowledge that can be used to transform the way addiction is prevented and treated. Specifically, researchers are engaged in a variety of behavioral, genetic, and electrophysiological experiments designed to understand the neuronal basis of behavior—from feeding to decision-making—to determine how these essential behaviors are disrupted in addiction. NIH is capitalizing on expanded knowledge of the underlying neurobiology and brain circuitry involved in addiction to reveal new candidate systems (e.g., cannabinoid) that may be promising targets for the development of medications to treat addiction and other disorders (e.g., pain). NIDA and NIAAA are also interested in understanding the functional implications of genetic variants and epigenetic changes (heritable changes that regulate gene expression without altering the DNA sequence) that have been identified to understand how genetic and environmental factors, such as chronic stress or exposure to drugs of abuse, contribute to risk and resilience for addiction. Recent studies reveal how exposure to drugs can produce epigenetic changes in the germline, or reproductive cells, that can be transmitted across multiple generations through both maternal and paternal lines.

In terms of genetics, research shows that about 50 percent of an individual's risk of addiction depends on his or her genes and the dynamic interactions between genetics and the environment. Locating and identifying the individual genes that affect risk for substance use and addiction can help inform tailored prevention approaches and identify targets for medications development. A compelling example was the discovery of a cluster of nicotinic acetylcholine receptor genes on chromosome 15, implicated in early initiation of smoking, the transition to nicotine dependence, and vulnerability to lung cancer and peripheral artery disease.[593] The *alpha 5* nicotinic receptor gene within this cluster was identified as a potential medication target and shown to be involved in nicotine's aversive properties (e.g., withdrawal symptoms, which are a major trigger of relapse in tobacco users).

Identifying and Preventing Substance Abuse and Addiction

NIDA is supporting research designed to uncover neural markers of risk and protection that influence brain development and substance use trajectories. For example,

[590] http://www.drugabuse.gov/about-nida/strategic-plan/2010-strategic-plan.
[591] http://www.niaaa.nih.gov/sites/default/files/StrategicPlan.doc.
[592] http://addictionresearch.nih.gov/.

[593] Munafò MR, et al. *J Natl Cancer Inst.* 2012;104(10):740–8. PMID:22534784.

using functional MRI (fMRI), the brain can be scanned in its resting state to generate maps of regions that operate together (i.e., functionally connected). Recently created resting state fMRI maps of healthy volunteers will help establish critical benchmarks against which researchers will be able to compare patients with brain disorders or identify those at greater risk for addiction and other psychiatric disorders based on telltale "signatures." Such signatures, or "biomarkers," could become the basis of new diagnostic approaches that allow for the early detection and/or monitoring of psychiatric disorders, including SUD.

Prescription drugs, primarily opioid pain medications, ranks second (after marijuana) among the most commonly abused drugs. Notably, unintentional poisoning deaths involving prescription pain relievers more than quadrupled from 1999 through 2011 and now outnumber combined deaths involving heroin and cocaine. NIDA supports a variety of strategies to prevent prescription drug abuse, including epidemiological studies of the patterns, trends, and motivations underlying prescription drug abuse; development and testing of prevention interventions that have an impact on prescription drug abuse; studies of the effectiveness and impact of prescription drug monitoring programs; and development of pain medications with diminished abuse potential. The latter could result in reduced diversion (the use of prescription drugs for recreational use) and abuse (and thus availability) of highly addictive opioid medications.

Adolescents are particularly vulnerable to the negative impacts of substance use and misuse. Research has shown that early use of alcohol, tobacco, marijuana, and other substances not only increases risk for addiction to that substance, but also may affect risk for addiction to other substances as well as risk for long-term medical and social consequences. These substances target the brain, and given that brain development continues past adolescence into a person's twenties, these substances may interfere with brain development and have short- and long-term consequences on brain function. NIAAA-supported research is elucidating how alcohol exposure impacts the developing adolescent brain through a multisite longitudinal study of more than 800 youth ages 12–21, capturing them before and after they start to drink. Using a combination of advanced neuroimaging technology and neuropsychological and behavioral measures, the National Consortium on Alcohol and Neurodevelopment in Adolescence is assessing the effects of alcohol on brain development and associated cognitive, affective, and behavioral processes. The Consortium also is identifying brain characteristics and changes that may predict risk for developing alcohol use disorder. The study is laying the groundwork for future research on the impact of substance use on the developing brain.

NIH research also is focused on reducing college drinking and drug abuse and their many social and health consequences, including cognitive impairment, poor academic performance, physical and sexual assault, risky behavior, drug and alcohol poisoning, injuries, and death. NIAAA-supported research has yielded promising prevention strategies to intervene with harmful drinking and related consequences on college campuses. College presidents and administrators from across the nation have partnered with NIAAA to bring renewed national attention to college drinking. The NIAAA College Presidents Working Group encourages the translation of college prevention research findings into practice and provides a platform for sharing and disseminating evidence-based information. NIAAA and the Working Group are collaborating with extramural scientists on a "matrix" of interventions organized by effectiveness, cost, and ease of implementation to guide college administrators in selecting and implementing interventions for their campuses.

Early identification of young people at risk for, or already engaged in, alcohol and other drug use are key to the prevention of more serious problems later. NIAAA and NIDA will continue to promote and support research evaluating the effectiveness of screening, brief intervention, and referral to treatment, as well as other interventions for alcohol and other drug use in pediatric and primary care settings. For example, in FY 2012, NIAAA launched an initiative to evaluate its *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide in practice* and is supporting six studies that are evaluating the guide in a range of real-world settings. The brief, two-question screener is being assessed in youth ages 9–18 as a predictor of alcohol risk, alcohol use, and alcohol problems and as an initial screen for other behavioral health problems (e.g., other drug use, smoking, conduct disorder). To encourage use

of the youth alcohol screening guide, in FY 2013, NIAAA partnered with Medscape, a Web resource for physicians and health professionals, to provide continuing medical education for health care professionals. Additionally, NIDA researchers are developing and validating clinical tools for the screening and brief assessment of substance use severity for adolescents seen in pediatric medical settings. These tools will facilitate triaging adolescents into clinically relevant risk categories to guide the provision of prevention and treatment interventions.

Given that only a small percentage of individuals with alcohol or other drug problems ever seek treatment, NIAAA and NIDA are facilitating the implementation of screening and brief intervention for substance misuse into the primary health care setting. In addition to its youth screening guide, NIAAA continues to offer its *Clinician's Guide: Helping Patients Who Drink Too Much*[594] which provides screening, brief intervention, and referral to treatment guidelines for adults in primary care and mental health settings. Through the NIDAMED initiative[595]—NIDA's outreach to practicing physicians, physicians in training, and other health professionals—NIDA continues to encourage physician screening of tobacco, alcohol, and illicit prescription drug abuse. NIDA's Web-based Drug Use Screening Tool (now mobile and accessible via smartphones and tablets) provides a single-question quick screen to identify recent adult patient drug use, followed by the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test, which guides clinicians through a series of screening questions and, based on the patient's responses, generates a substance involvement score that suggests the level of intervention needed.

Developing Effective Treatments for Substance Use and Addiction

Despite the enormous burden that substance use and addiction exact on our society, few medications are approved yet to treat SUD. This disconnect has made the development of evidence-based pharmacotherapies a top priority for NIDA and NIAAA, which are both working to quicken the pace of clinical research and "de-risk" compounds so that they can become attractive to the pharmaceutical industry. A growing partnership between NIDA and NIAAA, especially for clinical research, will harness strengths and overlapping priorities related to SUD. Across a number of clinical trials, NIAAA and NIDA are incorporating DNA collection and analysis, paving the way to move treatment for SUD closer to personalized medicine.

To streamline the timely and costly process of developing alcohol medications, NIAAA established the NIAAA Clinical Investigations Group (NCIG) to test repurposed and novel candidate compounds rapidly in Phase II clinical trials in 12–18 months. NCIG recently completed a multisite clinical trial that showed the anti-smoking medication varenicline (Chantix®) significantly reduced alcohol consumption and craving in both smokers and nonsmokers with alcohol use disorder. Going forward, NCIG will test both repurposed and novel compounds often working in collaboration with extramural scientists and the pharmaceutical industry. NIAAA also supports promising pharmacotherapy research outside of NCIG. In an independent study, the widely prescribed medication gabapentin, used to treat pain epilepsy, reduced heavy drinking and other related symptoms in alcohol-dependent patients. A study to replicate the gabapentin finding within NCIG is anticipated.

To accelerate clinical trials for drug abuse medications development, NIDA is offering greater up-front support to grantees for a shorter period of time. This shift was prompted in part by the highly successful clinical trials of Probuphine, a buprenorphine medication implanted under the skin that allows continuous medication delivery for six months after a single treatment. Use of this medication is expected to improve prescription drug adherence (i.e., taking medications as directed) and reduce the possibility of abuse. Another strategy involves the recent development of a NIDA Intramural Medications Development Program that includes medicinal chemistry, in vitro and behavioral testing in preclinical models of substance abuse, neurochemistry, metabolism research, and pharmacokinetic analysis of novel medication candidates. Through this program, NIDA aims to accelerate the pursuit of medications to treat cocaine, methamphetamine, and marijuana use disorders.

Recent advances include the development of potential approaches for the treatment of smoking as well as cocaine and heroin addiction. NIDA-funded investigators have

[594] http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm.
[595] http://www.drugabuse.gov/medical-health-professionals.

developed a nicotine vaccine that induces the body to produce antibodies that can prevent nicotine from entering the brain. Although studies have demonstrated safety and proof-of-concept for nicotine vaccines, the vaccines' inability to generate a sufficiently strong immune response has hindered their success. Newer candidates stimulate higher immune response and improved vaccine potency and are thus showing great promise to combat nicotine addiction. In another research advance, a potential approach to treating cocaine addiction (or overdose) involves a naturally occurring enzyme called butyrylcholinesterase (BChE), which can metabolize, or convert, cocaine into other compounds. Researchers previously created BChE-based compounds with enhanced cocaine-metabolizing properties and now have developed a virus to deliver this compound. This virus showed promising results in cocaine-dependent animals; over a 6 month period, the animals did not engage in cocaine-seeking behavior even when primed with cocaine injections, and they still had high levels of the enzyme in their bodies at the end of the study.[596] NIDA researchers are also investigating the potential of a new, highly selective dopamine D3 receptor antagonist on cocaine use in multiple animal models. In addition, researchers from the NIDA Intramural Program and the Walter Reed Army Institute of Research successfully developed an anti-heroin vaccine in a mouse model. This vaccine has been shown to sequester heroin and its two main active metabolites in the blood. Thus, this vaccine not only has the potential to block the rewarding and reinforcing effects of heroin, but also potentially prevent heroin overdose.

Behavioral treatments continue to be a critical component of addiction treatment. For example, in the largest trial of its kind, NCI-funded researchers from the Fred Hutchinson Cancer Research Center found that telephone counseling using motivational interviewing and cognitive behavioral approaches significantly improved six-month smoking cessation rates in older teens. This finding is noteworthy, given that 20 percent of American high school seniors smoke cigarettes, and few strategies have been effective in sustaining cessation among teen smokers. NHLBI, NCI, and NIDA also have partnered to co-fund research on smoking cessation in hospitalized patients, and NCI recently funded two special initiatives to improve effectiveness of smoking cessation interventions among low-income adults and prevent and reduce smokeless tobacco use. Lastly, a NIDA-supported multisite randomized controlled clinical trial showed that a Therapeutic Education System, an Internet-delivered behavioral intervention using motivational incentives as a clinician-extender, can expand access and improve addiction treatment outcomes. NIDA is continuing to support research to expand the availability of behavioral therapies by developing interventions using alternative delivery formats, such as Web-, computer-, PDA- or text-based modalities, all of which may benefit hard-to-reach populations and increase access to treatment options for millions of smokers. Alternative delivery formats also have the potential to increase accessibility of behavioral interventions for alcohol misuse and alcohol use disorders; NIAAA will continue to explore the use of mobile technologies and other delivery formats to intervene with problem drinking for different populations.

NIDA's portfolio includes a significant investment in effectiveness and comparative effectiveness research that encompasses hospitals and primary care settings, community treatment programs, and the criminal and juvenile justice system, where drug abuse problems are widespread. NIDA's Drug Abuse Treatment Clinical Trials Network plays a key role in testing evidence-based treatments in community settings, optimizing their utility and cost-effectiveness and fostering their adoption.

Addressing the Medical and Social Consequences of Substance Use and Addiction

The study of the medical and social consequences of alcohol and other drug abuse and addiction requires a considerable continuing scientific investment in several areas. HIV/AIDS remains one of the most serious medical consequences of substance abuse and its link goes well beyond injection drug use, because intoxication or addiction often leads to impaired decision-making and risky sexual behaviors. Thus, NIAAA and NIDA support research to improve HIV prevention among alcohol and other drug users; enhance screening and treatment access for HIV/AIDS and other co-occurring conditions; and uncover and prevent any potential interactions between drugs of abuse, HIV/AIDS disease processes, and the medications used to

[596] Anker JJ, et al. *Biol Psychiatry*. 2012;71(8):700–5. PMID: 22209637.

treat both. The Adolescent Medicine Trials Network for HIV/AIDS Interventions, funded by NICHD, NIDA and NIMH, is actively exploring the interaction of substance use and HIV in at-risk adolescents and how to optimize prevention of such behaviors.

Similarly, research is now showing that HIV treatment is also HIV prevention in that patients treated with HAART not only have better health outcomes, but their decreased viral load and infectivity translates into decreased HIV transmission and incidence on a population level. A priority research area for NIH is to examine the effectiveness and potential scalability of the "Seek, Test, Treat, and Retain" strategy, which *seeks* out high-risk, hard-to-reach vulnerable populations (e.g., injection drug users), *tests* them for HIV, *begins treatment* in those who test positive, and *retains* patients in treatment and monitors their care. Large-scale studies have revealed a high prevalence of alcohol use and dependence among HIV-infected patients both in and out of care. NIAAA will continue to support research that develops and tests coordinated interventions to reduce alcohol use and alcohol-related consequences in HIV-impacted populations.

Virtually every organ system in the body is vulnerable to damage induced by excessive or chronic alcohol use, damage which results in a range of medical conditions that include liver disease, pancreatitis, heart disease, fetal abnormalities and brain damage. Liver disease claims 37,000 lives annually; alcohol is the underlying cause for approximately 40 percent of these deaths. Preventing, diagnosing, and treating alcoholic liver disease (ALD) remains an NIAAA priority. In FY 2012, NIAAA funded four research consortia to pursue both new and improved clinical approaches to treat alcoholic hepatitis, a severe form of ALD with a high mortality rate. To better understand how excessive drinking damages the liver, NIAAA intramural scientists developed a mouse model of ALD that more closely resembles the progression of the disease in humans. Studies using this model could uncover new targets for treatment of ALD and help researchers understand alcohol-induced damage to other organs.

NIAAA and NIDA are building on the substantial research progress made over the past 40 years in understanding and addressing the effects of alcohol and substance use on human health and well-being across the lifespan. Every hour, a baby is born suffering from opioid withdrawal, which can lead to multiple adverse maternal and neonatal consequences. Better treatment options could improve public health and reduce associated medical costs. To that end, a NIDA-supported study found that buprenorphine results in 43 percent less time in hospital, 60 percent shorter treatment duration, and 89 percent less morphine administered for withdrawal symptoms in neonatal abstinence syndrome compared to methadone. If buprenorphine were adopted as the standard of care for women of childbearing age, it could result in a savings of nearly $260 million per year.[597]

FASDs represent a broad array of physical and neurodevelopmental abnormalities—ranging from mild cognitive and growth abnormalities to severe developmental delays—caused by prenatal alcohol exposure. Understanding, preventing, and intervening with FASD has long been a priority of NIAAA. NIAAA emphases in this area include improving detection of harmful drinking during pregnancy through the development of reliable biomarkers; intervening with the symptoms and neurobehavioral consequences of FASD in affected children through nutritional supplementation, behavioral interventions, and other strategies; using 3-D facial imaging to identify children who are prenatally exposed but lack the hallmark facial features of fetal alcohol syndrome to facilitate early intervention; and conducting case ascertainment studies to more accurately establish the prevalence of FASD. In addition, NIAAA collaborates with NICHD and NIDCD in the Prenatal Alcohol and SIDS and Stillbirth (PASS) Network, which investigates the effects of alcohol and other substances on birth outcomes, including FASD and SIDS.

A cost–benefit analysis of the Communities That Care drug abuse prevention system found long-term reductions in drug use and other risky behaviors, as well as monetary benefits relative to the cost of conducting the intervention—a savings of between $5 and $10 for every $1 invested, with returns that increase over time. Benefits stem from anticipated reductions in smoking-related mortality, improved health, lower medical expenses, and lower criminal justice system and crime victimization costs over the life course of program participants.[598]

[597] Jones HE, et al. *N Engl J Med*. 2010;363(24):2320–31. PMID: 21142534.
[598] Hawkins JD, et al. *Arch Pediatr Adolesc Med*. 2012;166(2):141–8. PMID: 21969362.

SUD represent a significant problem for service members, veterans, and their families. These disorders frequently co-occur with PTSD because many individuals may use alcohol and other drugs to alleviate anxiety, depression, and other symptoms associated with PTSD, thus complicating treatment for both conditions. NIAAA participates with NIDA in the National Research Action Plan to accelerate research in this area to facilitate earlier diagnosis and improve prevention and treatment. NIAAA will continue to support research to investigate the neurobiological relationships between alcohol use and PTSD and to develop behavioral interventions that address alcohol misuse and PTSD, particularly among service members and veterans.

Tobacco use is the single most preventable cause of death and disease in the U.S. Each year, more than 480,000 Americans die prematurely from tobacco-related illnesses. In addition, tobacco use costs the U.S. between $289 billion and $332.5 billion annually in direct medical expenses and lost productivity. Located in the NIH Office of Disease Prevention, the Tobacco Regulatory Science Program[599] coordinates the trans-NIH collaborative effort with FDA's Center for Tobacco Products to conduct research to support its regulatory activities over tobacco products. The Tobacco Centers of Regulatory Science[600] are the centerpiece of this NIH–FDA collaboration, and they provide a range of expertise, including epidemiology, economics, toxicology, addictions, and marketing. In addition, NIDA supports innovative research on how altering nicotine levels in tobacco products could affect the way people might use tobacco and become addicted.

Age-related Macular Degeneration

Age-related macular degeneration (AMD) gradually destroys sharp, central vision. As the leading cause of irreversible blindness in older Americans, AMD will impose an increasing burden in future years as the baby boomer generation ages. AMD affects patients' ability to read, recognize faces, drive a car, or perform even simple tasks that require hand-eye coordination. It severely restricts mobility, forcing many otherwise healthy seniors to prematurely lose their independence and ultimately to be cared for in costly assisted-living facilities. Approximately 7.3 million people in the U.S. are at risk of developing advanced, sight-threatening AMD in one or both eyes, 1.75 million currently have AMD, and nearly 3 million are expected to have AMD by 2020.[601]

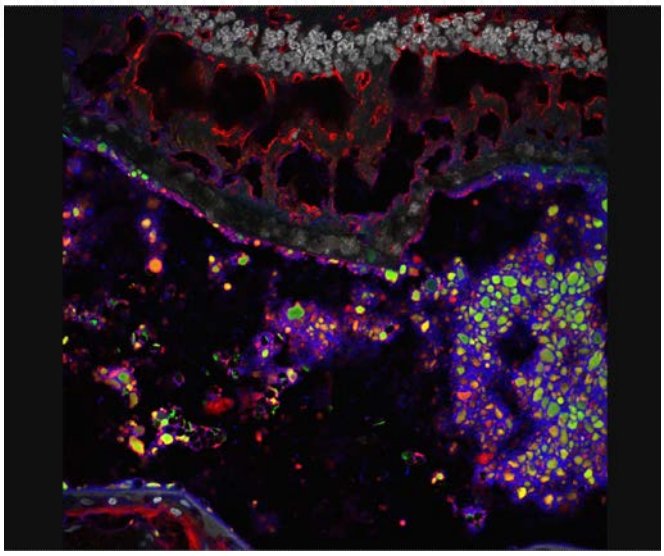


Figure 3-15. *Age-related macular degeneration with lipids (blue), fibulin-3 (green), and complement factor H (red) accumulated in lipid-rich deposits called drusen. Credit: Robert Fariss, Ph.D., Mercedes Campos, M.D., and Graeme Wistow, Ph.D., NEI.*

The early stage of the disease is characterized by small yellow deposits under the retina called drusen. In intermediate AMD, these small deposits become larger and may cause mild visual impairment. Advanced disease has two forms. Geographic atrophy (GA), commonly known as "dry" AMD, occurs when the retinal pigment epithelium (RPE), a layer of tissue that supports the neural retina, degenerates and destroys photoreceptors in the macula, the central portion of the retina that allows us to see fine visual detail and colors. Neovascular, or "wet," AMD is marked by abnormal blood vessels growing under the retina, which leaks blood and fluid into the macula. Both forms can lead to severe visual impairment.

The Age-Related Eye Disease Study (AREDS) funded by NEI was a clinical trial that demonstrated that a particular combination of antioxidant vitamin and mineral supplements (the AREDS formulation) reduced the progression to

[599] https://prevention.nih.gov/tobacco-regulatory-science-program.
[600] https://prevention.nih.gov/tobacco-regulatory-science-program/research-portfolio/centers.

[601] Friedman DS, et al. *Arch Ophthalmol*. 2004;122(4):564–72. PMID: 15078675.

advanced AMD by about 25 percent. Building on these landmark findings, AREDS2 tested a new formulation, adding omega-3 fatty acids as well as substituting antioxidants lutein and zeaxanthin for beta-carotene, which has been implicated as a risk factor for lung cancer in smokers and former smokers. While the omega-3 fatty acids had no effect on the formulation, the combination of lutein and zeaxanthin was a successful substitution, and this new formulation provides a safe and effective treatment for people at risk of advanced AMD.[602]

The NEI-funded Comparison of AMD Treatments Trials found that the drugs Avastin and Lucentis were equally effective for improving visual acuity in AMD. While Genentech designed Lucentis to treat AMD, Genentech's cancer drug Avastin also blocks the growth of abnormal blood vessels and the subsequent fluid leakage from the faulty vessels. Clinicians found that administering Avastin off-label for AMD not only was an effective treatment, but it also was much cheaper than Lucentis. The clinical trial also compared monthly and as-needed treatment schedules. After two years of treatment, visual acuity with monthly treatment was slightly better than with as-needed dosing, regardless of the drug. Switching to as-needed treatment after one year of monthly treatment yielded outcomes nearly equal to those obtained with as-needed treatment for the full two years.[603]

While investigators compare promising therapeutic options for neovascular AMD, no approved therapies exist for GA due to the lack of molecular targets. However, scientists have been piecing together the molecular mechanisms that trigger atrophy. In 2012, NEI investigators found that an extracellular signaling protein, ERK1/2, activates a series of biological events that lead to the death of RPE cells in GA. In a mouse model of GA, inhibition of ERK1/2 prevented RPE cell death, suggesting a potential therapy to prevent GA.[604]

Further research into the molecular mechanisms in AMD has led to studies of DNA methylation, a chemical modification of DNA that interrupts gene expression. DNA methylation can be altered by environmental exposures and gene variants. NIH investigators found that patients with AMD had reduced DNA methylation for a particular gene (interleukin-17 receptor C [*IL17RC*]) compared to patients without AMD, which caused greater IL17RC protein production. This protein enhances immune responses to infections, such as fungal attacks. While the immune system normally protects cells, uncontrolled immune activity may damage retinal tissues and lead to AMD. The investigators plan to determine if these changes are caused by something in the environment and find therapies to reverse the changes.[605]

The AMD Gene Consortium, an international network of 18 laboratories supported by NEI, conducted the largest GWAS of AMD and found 7 new gene variants for the disease while confirming another 12 variants identified in previous GWAS.[606] Some of these gene variants are found in the cholesterol pathway. In AMD, cholesterol is known to accumulate in the eye; macrophage cells play a key role in clearing cholesterol from the eye, but they become less efficient with age. Eye drops containing a type of drug known to promote cholesterol release from macrophages, called a liver X receptor (LXR) agonist, helped restore macrophage function and prevent AMD progression in a mouse model.[607]

Blood Diseases

NIH supports research on the causes, prevention, and treatment of nonmalignant blood diseases, including anemias, sickle cell disease (SCD), and thalassemia; premalignant processes such as myelodysplasia and myeloproliferative disorders; hemophilia and other abnormalities of hemostasis and thrombosis; and immune dysfunction.

Chronic anemias result from a deficiency of red blood cells or an abnormality in hemoglobin production, as is the case with SCDs and Cooley's anemia. Patients 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.

[602] Age-Related Eye Diseases Study 2 Research Group. *JAMA*. 2013;309(19):2005–15. PMID: 23644932.
[603] CATT Study Group. *Ophthalmology*. 2012;119(7):1388–98. PMID: 22555112.
[604] Ambati J, et al. *Proc Natl Acad Sci U S A*. 2012;109(34):13781–6. PMID: 22869729.
[605] Wei L, et al. *Cell Rep*. 2012;2(5):1151–8. PMID: 23177625.
[606] AMD Gene Consortium. *Nat Genet*. 2013;45(4):433–9. PMID: 23455636.
[607] Apte RS, et al. *Cell Metab.* 2013;17(4):549–61. PMID: 23562078.

Efforts led by NIDDK include:

- Basic mechanisms involved in regulating the production and terminal development of blood cells (hematopoiesis) and in regulating the expression of genes relevant to normal blood cell maturation and function
- Regulatory molecules, cytokines, and hematopoietic growth factors that influence blood cell production from hematopoietic stem cells and progenitors
- Blood cell membrane structure and function relevant to the maintenance of blood cell integrity, the tissue localization of hematopoietic progenitor cells, and the circulation and survival of mature blood cells
- Acquired and congenital disorders of red blood cell production and survival (erythropoiesis), including anemias resulting from disturbances in the production or function of hemoglobin (e.g., thalassemias, SCD)
- The molecular biology of heme and hemoglobin synthesis and turnover
- The metabolism, storage, and transport of iron and disorders resulting from disturbances in these processes, such as hemochromatosis and iron-restricted anemias
- The metabolism, structure, and function of leukocytes (white blood cells) and myeloid progenitors
- Translational applications of new insights and knowledge gained from basic research in these areas toward the development of novel or improved approaches for the diagnosis, stratification, and treatment of hematologic diseases, with a particular emphasis on the development of disease biomarkers, gene-targeted therapies, hematopoietic stem cell transplantation (HSCT) in heritable blood diseases, and the measurement and chelation of tissue iron in iron overload disorders

In 2012–2013, NIDDK-supported research advanced a potential new treatment strategy for iron overload anemias such as hereditary hemochromatosis. Hepcidin is a protein that regulates iron balance in humans and other mammals by reducing dietary iron absorption into the body. Insufficient levels of hepcidin cause or contribute to iron overload anemias. New research demonstrated that a miniature form of hepcidin—PR65—significantly reduced blood iron levels for up to 24 hours in mice lacking hepcidin while fed a diet high in iron.[608] Other advances relate to potential treatments for Diamond-Blackfan anemia, an inherited form of bone marrow failure, and myelodysplastic syndrome, an acquired disease arising from a deletion of a portion of chromosome 5 [del(5q) MDS]. NIDDK-supported research has shown that nutritional supplements can mitigate the severity of these two serious forms of anemia in an experimental model.[609]

Medical advances have extended the life expectancy of patients with SCD from childhood, in the 1970s, to 40–60 years of age today. Research has shown that reactivation of fetal hemoglobin—which is typically replaced by adult hemoglobin within the first year after birth—can treat red blood cell diseases like SCD. Based on results of an NIH-supported clinical trial, hydroxyurea became the first agent approved by FDA for prevention of painful sickle cell episodes. In 2011, these results were expanded to children 9–18 months old in the NHLBI-supported Pediatric Hydroxyurea Clinical Trial (BABY-HUG). Results from a follow-up study to the BABY-HUG trial found that administering hydroxyurea therapy to infants and toddlers with SCD reduced hospitalization and cut medical costs by an estimated 21 percent annually.[610] These savings are estimated to increase as patients age and their symptoms increase in severity and frequency. NHLBI is taking a holistic, systems-based strategy to identify ways to pre-empt SCD progression, decrease the incidence of strokes and their impact among children with SCD, treat myriad complications that have arisen as patients with SCD are living longer, and ensure the implementation of effective treatments among the populations most in need.

Other priority research initiatives include the Stimulating Hematology Investigation: New Endeavors (SHINE) program,[611] which is intended to promote innovative, high-quality basic and translational hematology research where needs and opportunities for progress are particularly timely.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis, is a complex multisymptom condition characterized by overwhelming fatigue that does

[608] Ramos E, et al. *Blood*. 2012;120:3829–36. PMID: 22990014.
[609] Payne EM, et al. *Blood*. 2012;120:2214–24. PMID: 22734070.
[610] Wang WC, et al. *Pediatrics*. 2013;132:677–83. PMID: 23999955.
[611] http://grants.nih.gov/grants/guide/pa-files/PAS-13-031.html.

not improve with bed rest and that may be worsened by physical or mental activity. CFS is diagnosed two to six times more often in women than men. The condition is difficult to diagnose because of multiple diagnostic criteria used by various practitioners as well as a lengthy timeframe for occurrence and recurrence of the symptoms. CDC states that in order to be diagnosed with CFS, a patient's symptoms must have persisted or recurred during six or more consecutive months of illness.

The etiology of CFS is unknown, and no specific diagnostic tests are available. Moreover, since many illnesses have incapacitating fatigue as a symptom, care must be taken to exclude other known and often treatable conditions before a diagnosis of CFS is made. Treatment programs are individualized and are based on a combination of therapies, such as traditional and alternative therapies, which address symptoms, activity management, and coping techniques.

Several other ICs support research in this field. NCI supports intramural and extramural research on viruses linked to both cancer and CFS, in addition to research on mechanisms underlying pain and fatigue in cancer, which may have applications to these symptoms in CFS. CFS and cancer research primarily overlap in possible common etiological agents such as viruses and environmental toxins, common systemic changes such as immunologic profiles and cytokine levels, and common symptom clusters such as pain and fatigue.

NHLBI has funded several investigator-initiated research projects predominately examining circulatory dysfunction, orthostatic intolerance, and autonomic nervous system in chronic fatigue. In addition, NINDS supports extramural CFS research directed at effects on the CNS, including the role of brain mast cells in CNS inflammation, cognitive behavioral stress management to improve symptoms, and categorization of subtypes of CFS, which could enable more focused research on this heterogeneous disorder to determine causes and develop targeted treatments.

NIH will continue to encourage research on CFS through two FOAs for research project grants (R01) and exploratory/developmental research grants (R21) titled Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment.[612, 613]

The Office of the Secretary of HHS has determined that an *ad hoc* working group be developed to outline the breadth and depth of the Department's activities on CFS and identify opportunities for interagency collaboration. The Deputy Assistant Secretary of Health – Women's Health and Director of the Office on Women's Health, Office of the Assistant Secretary for Health will lead and coordinate the development of the CFS strategy. The HHS Chronic Fatigue Syndrome Advisory Committee will continue to provide advice and recommendations to the Secretary of HHS via the Assistant Secretary for Health of HHS on issues related to CFS.[614]

Cystic Fibrosis

Cystic fibrosis (CF) is an inherited, autosomal recessive disease of the secretory glands, including the glands that make mucus and sweat. The disease is caused by mutations in the gene for CF transmembrane conductance regulator (CFTR), which codes for an ion channel. CF primarily affects the lungs, pancreas, liver, intestines, sinuses, and sex organs. For example, thick mucus accumulates in the lungs and blocks the airways, thereby rendering CF patients susceptible to repeated bacterial infections that can severely damage the lung. Respiratory failure due to bacterial infection is the most common cause of death among CF patients. Mucus blockage of the pancreatic ducts can cause vitamin deficiency and malnutrition. In addition, CF patients lose large amounts of salt when they sweat, which can lead to dehydration, increased heart rate, tiredness, weakness, decreased blood pressure, and heat stroke.

Improved treatments have led to a dramatic increase in the life expectancy of people with CF, which is now approximately 37 years old, although some people are living well into their 40s, 50s, or older. Digestive complications of the disease, however, often interfere with normal growth and weight gain for children with the disease. NIDDK is currently funding the Baby Observational and Nutrition Study of Cystic Fibrosis to investigate the appropriate diet for newborns with CF. Research has found, however, that as more and more people with CF reach adulthood, about half will develop CF-related diabetes, an unusual form of diabetes that can lead to deterioration of lung function and a poorer prognosis. Thanks to NIH-supported research, we

[612] http://grants.nih.gov/grants/guide/pa-files/PAR-12-032.html.
[613] http://grants.nih.gov/grants/guide/pa-files/PAR-12-033.html.

[614] http://www.hhs.gov/advcomcfs/.

now know that insulin therapy helps people with CF-related diabetes maintain their body weight, improve lung function, and feel healthier.

Over the past two decades, CF research has improved greatly our understanding of CFTR regulation at the molecular level, demonstrated the functional consequences of CFTR defects at the cellular level, and led to the development of several new experimental therapies. Many abnormalities have been characterized in CF, including defects in ion transport, innate immunity, airway hydration or clearance, and excessive inflammation, but which of these factors is key to morbidity and mortality and how these abnormalities are interrelated remain unknown.

NHLBI-supported investigators studying the molecular basis of CF have found that an epithelial sodium channel, called ENaC, becomes hyperactive in CF, which leads to a decrease in the volume of the liquid normally found on the surface of airways and a lowering of its pH. The investigators also identified a protein that inhibits ENaC, suggesting a therapeutic strategy that may restore airway surface liquid volume, normalize its pH, and improve lung function for patients with CF.[615]

Another study by NHLBI-supported investigators using the recently developed pig model of CF, showed that low pH in the thin layer of liquid that coats the airways appears to reduce the killing of bacteria. These results link the genetic defect in CF to a defect in host defense mechanisms and may explain why CF patients tend to get bacterial colonization of their airways. Recognizing that the pH problem was caused by diminished transport of bicarbonate by CFTR, investigators were able to show that delivering a solution of sodium bicarbonate (the chemical in baking soda) to the pig lungs increased secretion of host defense factors and bacterial killing in their airways. If the same thing can be done safely in humans, it may be possible to prevent many of the bacterial infections that complicate CF.[616]

Chronic unremitting airway infection and inflammation result in progressive lung damage that culminates in respiratory failure and premature death in CF. Excessive mucus production contributes to the pathogenesis of a number of airway diseases including CF. Recent findings in mouse models have shown that Muc5B, one of the principal macromolecules in airway mucus, is required for mucociliary clearance, for controlling infections in the airway, and for maintaining immune homeostasis in the lungs. Hence, targeted therapies to enable adequate Muc5B expression may enhance mucociliary clearance and airway defense.[617] In addition, despite increasing awareness of the polymicrobial nature of lung infection in CF, we do not have a good understanding of how the composition and structure of the airway microbial community influences the course of lung disease in CF. NHLBI-supported research took advantage of an extensive collection of mucus samples from several hundred CF patients and revealed critical relationships among airway bacterial community structure, disease stage (early, intermediate, or advanced lung disease), and clinical state (baseline health, exacerbation of symptoms, receiving treatment for exacerbation, or recovering from treatment). This study also identified antibiotic use as the primary driver decreasing bacterial diversity with age and decreasing lung function.[618]

A high priority for CF research is understanding the basic underlying disease mechanisms to inform the development of more targeted treatments. For example, while more than 2,000 variants of the human *CFTR* gene are known, only 23 of these variants previously had been confirmed to cause CF. New research raises the total of confirmed CF-causative alleles to 127. These findings will improve genetic testing for people with CF and their families.[619]

Until recently, CF treatments were restricted primarily to relieving symptoms and improving quality of life. Direct modulation of the underlying pathophysiological mechanisms of CF—long a therapeutic goal of researchers—has become a reality, albeit for only a minority of patients. An oral drug, marketed as Kalydeco®, was approved by FDA in 2012. Although ineffective for most people with CF, the medication has been found to be safe and to confer considerable improvement in the function of the defective ion channel in people with an uncommon *CFTR* mutation. Ongoing efforts include taking similar

[615] Garland AL, et al. *Proc Natl Acad Sci U S A*. 2013;110(40):15973–8. PMID: 24043776.
[616] Pezzulo AA, et al. *Nature*. 2012;487:109–13. PMID: 22763554.
[617] Roy MG, et al. *Nature*. 2014;505(7483):412–6. PMID: 24317696.
[618] Zhao J, et al. *Proc Natl Acad Sci U S A*. 2012;109(15):5809–14. PMID: 22451929.
[619] Sosnay PR, et al. *Nat Genet*. 2013;45(10):1160–7. PMID: 23974870.

approaches to identify medications that may benefit patients with the more common *CFTR-deltaF508* mutation. Although several candidate small molecule drugs have been found to improve stability of the *CFTR-deltaF508* protein product, none has been efficacious by itself. New research funded by NIDDK defines three classes of corrector compounds. Existing correctors (Classes I and II) do not fully stabilize the first nucleotide-binding domain, but the role of this third corrector class can be fulfilled with glycerol or other "chemical chaperones." Combining all three corrector classes achieved approximately wild-type levels of chloride channel function in cultured human lung cells bearing the CFTR-deltaF508 mutation; using only one or two classes of correctors yielded much lower activity.[620]

Transplantation

Since the first successful kidney transplant between identical twins in 1954, transplantation has become the treatment of choice for end-stage organ failure. Despite tremendous progress, however, major barriers still remain to the overall success of transplantation, including immunological incompatibility between donor and recipient, acute rejection, chronic graft dysfunction, and complications from requisite long-term use of immunosuppressive drugs. NIH supports basic and clinical research that focuses on the immunologic processes underlying transplant rejection and acceptance, ways to reduce or eliminate the need for immunosuppressive drugs, and the development of new, less toxic anti-rejection therapies.

Hematopoietic stem cell transplantation (HSCT) can be an effective treatment for a number of malignant and nonmalignant blood, bone marrow, or immune system disorders. However, the development of graft versus host disease (GVHD), in which the transplanted cells attack the recipient's body, remains a major cause of morbidity and mortality and thus limits the clinical utility of the transplant procedure. Approximately 50 percent of those receiving cells from a donor (as opposed to their own cells) develop acute GVHD. High-dose systemic glucocorticoids, which act to suppress the immune system, are the standard of care treatment for GVHD. However, the response to therapy is variable and difficult to predict. NIH is funding work to identify biomarkers that can be used in diagnostic tests for both GVHD and resistance to steroid therapy, thus improving outcomes via early detection and efficient treatment of GVHD. For example, a recent NIH-funded study found that higher plasma levels of the biomarker Suppressor of Tumorigenicity 2 (ST2) was associated with treatment resistance and a four times greater likelihood of death within six months.[621] The development of diagnostics to predict the emergence of GVHD, as well as resistance to steroid therapy for the disease, has the potential to significantly impact the early detection and treatment of GVHD, resulting in improved outcome to HSCT.

Scientists have observed that some recipients of liver transplants from living donors who stop taking their immunosuppressive drugs because of other health problems have continued to have a well-functioning liver without rejection. In 2012, the results of an NIAID-sponsored clinical study to establish the feasibility of immunosuppression withdrawal in pediatric living donor liver transplant recipients were published, reporting that 60 percent of children in the trial were successfully weaned off immunosuppressive medication completely, with normal function of the transplanted tissue two years after drug withdrawal.[622] A larger trial is underway to determine whether these results can be replicated in a more diverse population.

Efforts also continue to improve the ability to monitor the status of a transplanted organ and determine the recipient's need for immunosuppressive drugs. The Clinical Trials in Organ Transplantation program, which began in 2004, recently identified two noninvasive tests for diagnosing and predicting kidney transplant rejection. The goal is to develop tests that are safer and more reliably accurate than kidney biopsy, currently the gold standard for diagnosing rejection. One study identified three RNA molecules present in urine that provided a clinically useful diagnostic and predictive signature of kidney rejection. Another study identified a urinary protein that distinguishes people at low risk of developing kidney rejection from those at high risk. These results are an important step toward individualized care for transplant recipients and the ability to reduce immunosuppressive therapy safely.

[620] Okiyoneda T, et al. *Nat Chem Biol*. 2013;9(7):444-54. PMID: 23666117.

[621] Vander Lugt MT, et al. *N Engl J Med*. 2013;8;369(6):529–39. PMID: 23924003.

[622] Feng S, et al. *JAMA*. 2012;307(3):283–93. PMID: 22253395.

As a result of HAART, people in developed countries who are diagnosed with HIV infection early in the course of the disease have a life expectancy of 75 years and may develop conditions treatable by kidney transplantation. The NIAID-sponsored Solid Organ Transplantation in HIV: Multi-Site Study, which concluded in 2013, demonstrated that people with well-controlled HIV infection can have acceptable outcomes after kidney and liver transplantations and that more research is needed to determine the best immunosuppressive regimen for these patients. The study results led to the establishment of liver and kidney transplantation programs at participating institutions and at several other centers in the U.S. and Europe for people with HIV and advanced organ failure. In addition, this study helped establish clinical management guidelines for HIV-infected kidney and liver transplant recipients and ultimately contributed to the 2013 HOPE Act, which opened the door for HIV-infected individuals to donate their organs to other HIV-infected patients requiring organ transplantation.[623]

Each day, 22 people in the U.S. die for lack of a donor organ. However, older Americans are particularly affected; in 2013, more than 60 percent of transplant recipients and approximately 66 percent of individuals waiting for an organ were age 50 or older.[624] In 2012, NIA led NIH in a new partnership with HRSA to raise awareness about organ donation among older Americans and to encourage them to register as potential donors.

NIH will continue to support transplantation research along the entire spectrum from basic discovery to Phase III clinical trials. In addition to a portfolio of investigator-initiated research projects, NIAID supports solicited research through cooperative groups. The Genomics of Transplantation Cooperative Research Program examines how patterns of gene expression and individual genetic variations are associated with clinical transplant outcomes. The HLA Region Genomics in Immune-Mediated Disease Research Consortium focuses on understanding the association between variations in the human leukocyte antigen (HLA) genetic region and immune-mediated diseases, including transplantation rejection and graft failure. The Nonhuman Primate Islet/Kidney Transplantation Tolerance program serves as a pipeline to NIAID-sponsored clinical trials by evaluating the safety and efficacy of existing and new therapeutics that can help transplant recipients tolerate transplanted tissues and have improved long-term outcomes. Programs for human transplantation studies include the Clinical Trials in Organ Transplantation and Clinical Trials in Organ Transplantation in Children consortia; The Transplantation in HIV study; the RELIVE Consortium, which studies the outcomes of living organ donors; The Clinical Islet Transplant Consortium; and the Immune Tolerance Network, a program that evaluates novel, tolerance-inducing therapies for transplantation as well as autoimmune diseases and asthma.

[623] Harbell J, et al. *Curr HIV/AIDS Rep*. 2013;10(3):217–25. PMID: 23893004.
[624] http://www.organdonor.gov/.

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 chronic and often rare illnesses due in part to an inappropriate immune system response that leads the body to attack its own organs, tissues, and cells. Some of these diseases may be triggered by an infectious agent or an environmental exposure, especially in individuals who have inherited susceptibility. In the U.S., between 14.7 million and 23.5 million individuals are affected by autoimmune diseases, with women disproportionately affected. An estimated 75 percent of rheumatoid arthritis (RA) cases are women; systemic lupus erythematosus (SLE), or lupus, afflicts African-American women four times more often than Caucasian women; and Caucasians are more than twice as likely as other races to develop multiple sclerosis (MS) and, in general, MS is almost twice as likely to affect women.

NIH recognizes the need to take action to increase knowledge and reduce the rising impact of autoimmune diseases. NIH is committed to advancing the understanding of how autoimmune diseases develop and to applying results of basic research to improve the health and quality of life of patients affected by these diseases.

The most common of these diseases include SLE, MS, type 1 diabetes, autoimmune thyroid diseases, myasthenia gravis, scleroderma, IBDs (such as Crohn's disease and ulcerative colitis), and RA. Organ-specific autoimmune diseases are characterized by immune-mediated injury localized to a single organ or tissue—for example, the pancreas in type 1 diabetes and the CNS in MS. (More information about NIH research on MS and diabetes is available in the "Neuroscience" and "Diabetes" sections in this chapter.) In contrast, non–organ-specific diseases, such as SLE, are characterized by immune reactions against many different organs and tissues, which may result in widespread injury.

Autoimmune diseases can affect any part of the body and have myriad clinical manifestations that can be difficult to diagnose. Genetic traits may enhance susceptibility to many of these diseases, so that a patient may suffer from more than one autoimmune disorder or multiple autoimmune diseases may occur in the same family. Furthermore, scientists suspect that hormones may play a role in the development of at least some autoimmune disorders. For these and other reasons, autoimmune diseases are best recognized as a family of related disorders that must be studied together as well as individually.

Although treatments are available for numerous autoimmune diseases, cures have yet to be discovered and patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, and hospitalization. The social and financial burdens of these diseases are immense and include poor quality of life, high health care costs, and substantial loss of productivity.

NIH supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH Institutes conduct and support autoimmune disease research, often in collaboration with professional and patient advocacy organizations. The congressionally mandated Autoimmune Diseases Coordinating Committee, chaired by NIAID, facilitates trans-Institute collaboration and cooperation with twice yearly meetings devoted to discussion of autoimmune diseases research programs.

NIH Funding for Autoimmune Diseases Research

NIH funding for autoimmune diseases research was $867 million in FY 2012 and $821 million in FY 2013.[625]

Summary of NIH Activities

Collectively, NIH-funded research seeks to understand the onset and progression of more than 80 types of autoimmune diseases and to use that knowledge to develop better strategies for disease prevention, diagnosis, and treatment. Research on these diseases is funded by a number of ICs and OD offices. For example, because autoimmune disorders disproportionately affect girls and women, ORWH partners with NIH ICs to support this research.

[625] http://report.nih.gov/categorical_spending.aspx.

NIAID-supported research on autoimmune diseases focuses on the immunologic basis of disease, including the fundamental immunologic principles underlying disease onset and progression, development of improved animal models of disease and diagnostic tools, and identification and evaluation of more effective immune-based treatments and prevention strategies.

Nine NIAID Autoimmunity Centers of Excellence,[626] co-sponsored by ORWH, enable partnerships among clinicians and basic researchers and conduct collaborative research, including clinical trials and mechanistic studies of immunomodulatory therapies. Their goal is to facilitate the identification of effective tolerance induction and immune modulation strategies to prevent or treat disease and accelerate the translation of scientific advances to the clinic. Research at the Centers focuses on lupus, Sjögren's syndrome, RA, MS, ulcerative colitis, and scleroderma. In 2012 and 2013, researchers completed three clinical trials, including one that evaluated the treatment of mildly active RA with lovastatin,[627] one that evaluated the change in the interferon signature with use of vitamin D in people with SLE who were vitamin D deficient,[628] and another trial that looked at the difference in the mechanism of action between two biologic therapies, etanercept and adalimumab, in subjects with RA who were just starting treatment.[629] The Centers also have published several articles that provide more detailed understanding of kidney inflammation, neutrophils, and interferon in human lupus as well as human Treg cells in healthy subjects and in subjects with type 1 diabetes.[630, 631]

The NIAID Immune Tolerance Network[632] evaluates novel, tolerance-inducing therapies for autoimmune diseases, conducts mechanistic studies to understand the cause of tolerance, and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in autoimmunity. Results from a recent Immune Tolerance Network study showed that treatment with intravenous rituximab and steroids is effective at inducing and maintaining disease remission for patients with anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis.[633] This is the first new treatment option for this patient population in more than 40 years.[634]

The Cooperative Study Group for Autoimmune Disease Prevention was renewed in 2012. Seven funded centers conduct research on common and disease-specific mechanisms of autoimmunity and on the development of new therapeutic targets and approaches to prevent autoimmune diseases (co-sponsored by NIDDK and JDRF, a foundation supporting type 1 diabetes research). In 2012–2013, the Cooperative supported 21 pilot projects that might lead to the development of novel targets for disease prevention or assays for biological markers of disease progression.

The HLA Region Genomics in Immune-Mediated Diseases Consortium is a cooperative research group that focuses on defining the association between variations in the human leukocyte antigen (HLA) genetic region and immune-mediated diseases, including autoimmune diseases (co-sponsored by NINDS). NIAID continues to support two trials to evaluate autologous hematopoietic stem cell transplantation for the treatment of scleroderma and MS, including mechanistic studies of these diseases and therapies.

In the NIAID IRP, scientists are conducting investigations of biological pathways that may be common to many autoimmune diseases, yielding fundamental information that will guide the development of novel therapies for these diseases. NIAID investigators are also exploring genetic and environmental factors, including infection, that affect the development of autoimmune diseases. Examples of NIAID IRP research include:

- Studies of the function of immune cells called T-regulatory, or Treg, cells, which suppress autoreactive cells that are capable of causing autoimmune disease. These studies are focused on specific mechanisms by which Tregs prevent the development of autoimmune disease and whether Tregs can reverse the course of autoimmune disease once it has started. In addition,

[626] http://www.autoimmunitycenters.org/mission.php.
[627] https://clinicaltrials.gov/ct2/show/results/NCT00302952.
[628] https://clinicaltrials.gov/ct2/show/study/NCT00710021.
[629] https://clinicaltrials.gov/ct2/show/study/NCT00837434.
[630] Baumjohann D, et al. *Nat Immunol*. 2013;14(8):840–8. PMID: 23812098.
[631] Jeker LT, et al. *PLoS One*. 2013;8(5):e66282. PMID: 23741528.
[632] http://www.immunetolerance.org/.
[633] Specks U, et al. *N Engl J Med*. 2013;369(5):417–27. PMID: 23902481.
[634] http://www.niaid.nih.gov/news/newsreleases/2013/Pages/VasculitisTherapy.aspx.

NIAID is working with industry to develop panels of immunomodulatory monoclonal antibodies that target human Tregs and will be used to up- or down-regulate Treg function. Manipulating Treg function is a major target area for new therapeutic approaches to treat autoimmune disease.

- Studies to determine whether antigens, the substances that trigger an immune response, will induce the programmed death of activated T cells that cause autoimmunity.
- Investigation of the immune responses and resulting diseases at mucosal surfaces of the respiratory, GI, and urogenital tracts. These studies have led to new insights into the causes of and new treatments for Crohn's disease and ulcerative colitis.
- Elucidation of the interacting genetic and environmental factors that give rise to systemic autoimmune diseases, such as lupus, arthritis, and systemic sclerosis (scleroderma).
- Studies of autoimmune lymphoproliferative syndrome, an inherited disorder of the immune system that causes enlargement of the lymph nodes, spleen, and liver due to an accumulation of immune cells in those organs. This syndrome can cause low red blood cell, platelet, and neutrophil counts.
- A Phase I clinical trial to test whether rituximab is a safe and effective treatment for anticytokine autoantibody-associated diseases.

NIDDK funds a wide range of research on type 1 diabetes, IBD, celiac disease, and other autoimmune diseases. For example, Type 1 Diabetes TrialNet (see the "Diabetes" section in this chapter) is an international network of researchers who are exploring ways to prevent, delay, and reverse the progression of type 1 diabetes. Another example is the NIDDK-supported Methotrexate Response in Treatment of Ulcerative Colitis trial, which was launched in 2012 to investigate the therapeutic value of methotrexate in adult ulcerative colitis patients for whom established therapies have failed.

The NIDDK Inflammatory Bowel Disease Genetics Consortium[635] is a major driver of the Institute's IBD research program. The Consortium provides support and resources to enhance gene discovery and uncover the role that genetics plays in these complex diseases. For example, the Consortium has used GWAS of adult and pediatric populations over the past several years to uncover a number of genetic variants associated with ulcerative colitis and Crohn's disease. Researchers, including those in NIDDK's IBD Genetics Consortium, recently identified 71 new genetic regions associated with IBD, raising the total number of known IBD susceptibility gene regions to 163, the largest number reported to date for a complex disease.[636] Finding new genetic variants will help scientists discover the molecular pathways that contribute to these diseases and can lead to new therapeutic targets.

Celiac disease is a condition in which there is an abnormal immune reaction to eating gluten—a protein in wheat, rye, and barley—whereby a person's immune system responds by attacking and damaging the lining of the small intestine. NIDDK-supported researchers have shown that delaying gluten exposure until at least 12 months of age in infants at risk for celiac disease may help delay its onset. The study showed differences between the developing gut microbes of infants with genetic predisposition for celiac disease and infants with a nonselected genetic background. Future research could potentially identify biomarkers to predict the development of celiac disease in at-risk individuals. These predictions could also lead to interventions that would potentially prevent the onset of celiac disease.[637]

NIDCR conducts research on Sjögren's syndrome, a chronic autoimmune disease in which white blood cells attack the body's own salivary and tear glands, decreasing production of saliva and tears and resulting in significant oral and ocular disease and discomfort. NIDCR's Sjögren's Syndrome Clinic develops new therapies, addresses unmet clinical needs, bridges traditional medical specialties, and fosters close collaboration between clinical and basic scientists focused on the disorder.

In addition, NIDCR intramural scientists have been studying salivary gland microRNAs, which are a type of ribonucleic acid that regulate gene expression. In comparing microRNA profiles of healthy people with those who have Sjögren's syndrome, the scientists identified a microRNA produced by

[635] http://ibdgc.uchicago.edu/.

[636] Jostins L, et al. *Nature*. 2012;491(7422):119–24. PMID: 23128233.
[637] Sellitto M, et al. *PLoS ONE*. 2012;7(3):e33387. PMID: 22432018.

the Epstein-Barr virus that might secrete the viral microRNA that is mistakenly internalized by salivary cells. The scientists found that the viral microRNA disrupted normal saliva secretion by shutting down a key step in calcium signaling. This study is the first to show that a viral microRNA can contribute to a systemic autoimmune disease, and this microRNA could be developed into a much-sought-after biomarker that allows clinicians to more easily diagnose Sjögren's syndrome. NIDCR, with support from NEI and ORWH, also sponsored the Sjögren's Syndrome International Collaborative Clinical Alliance.[638] In 2012, this international research team published new classification criteria for Sjögren's syndrome, based solely on objective clinical tests, which will be used to confirm diagnoses and classify patients in clinical studies.[639] NIDCR is supporting a number of other studies related to Sjögren's syndrome, including the validation of salivary diagnostic biomarkers to developing a noninvasive diagnostic test, research on the inflammatory cells that infiltrate the salivary gland,[640, 641] and the identification of genetic factors using GWAS.

A dry mouth disorder caused by a loss of salivary gland secretion is a common side effect in patients receiving radiation treatment for head and neck cancers. Currently no treatment is available for these patients. NIDCR Intramural scientists have conducted a Phase I clinical trial to test the safety and efficacy of delivering the water channel aquaporin-1 (AQP1) to salivary glands of patients who previously received radiation and suffer from dry mouth conditions. This study showed that the delivery of AQP1 is safe and that it relieved dry mouth symptoms in a subset of participants. Based on the success of this strategy, another clinical trial is being initiated that will use a delivery method that may be better tolerated by the patients and have longer-lasting treatment effects. Another study discovered a protein that is important to stimulate salivary gland production, and this protein is being used in gene therapy studies in mice to prevent the loss of salivary gland function caused by irradiation.[642] These therapies also may be useful to alleviate the symptoms of individuals with Sjögren's syndrome.

Autoimmune sensorineural hearing loss (ASNHL) is caused by the body attacking and destroying its own sound-detecting and balance-maintaining tissues in the inner ear. Although this condition produces progressive hearing loss and/or dizziness in both ears, it is potentially reversible. ASNHL is most likely caused by genetic and environmental interactions. The autoimmune destruction may begin in the ear itself (i.e., organ specific) or it may be a consequence of a systemic autoimmune disorder, such as SLE or RA. ASNHL is most commonly treated with powerful anti-inflammatory steroids called glucocorticoids, and the treatment usually restores some hearing. Unfortunately, long-term use of these drugs is associated with significant side effects, such as susceptibility to infection, hypertension, osteoporosis, cataracts, nervousness, and insomnia. Encouraged by the success of immunosuppressive drugs to treat RA and cancer, doctors have been substituting them for long-term treatment with glucocorticoids. An

[638] http://sicca.ucsf.edu/.
[639] Shiboski SC, et al. *Arthritis Care Res (Hoboken)*. 2012;64(4):475–87. PMID: 22563590.

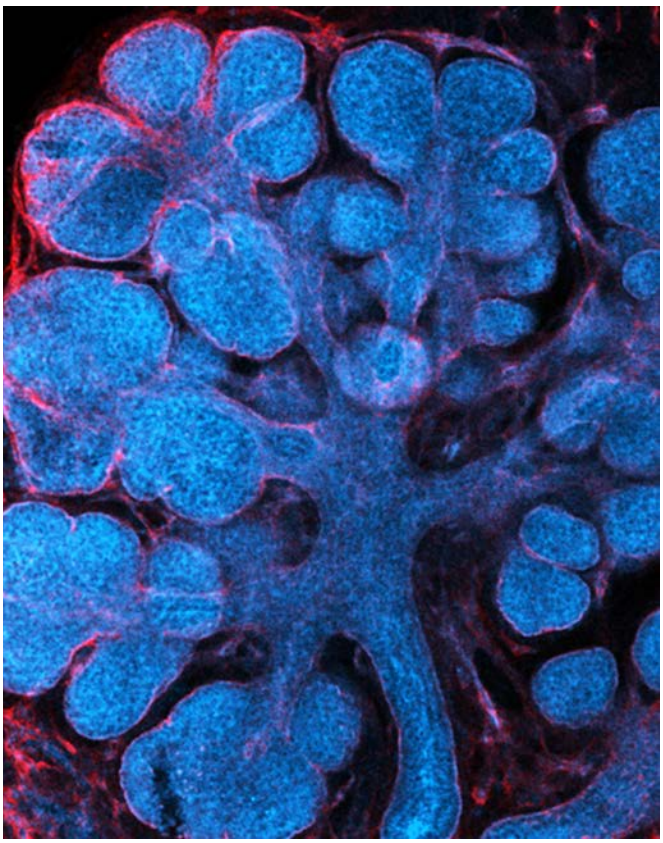


Figure 3-16. *An embryonic mouse salivary gland undergoing branching morphogenesis is visualized using myosin IIA (blue) and collagen IV (red). Credit: NIDCR.*

[640] Jin JO, et al. *Arthritis Rheum*. 2013;65(8):2132–42. PMID: 23666710.
[641] Lee BH, et al. *PLoS One.* 2013;8(1):e53113. PMID: 23382834.
[642] Knox SM, et al. *Nat Commun*. 2013; 4:1494. PMID: 23422662.

NIDCD-supported clinical trial for safety and efficacy tested another RA drug, called anakinra, to treat subjects with steroid-resistant ASNHL. Some patients who initially showed hearing improvements subsequently began to show symptoms of hearing loss. Consequently, the trial is now testing a longer-acting drug called gevokizumab. The gevokizumab Phase I clinical trial began in 2013 and will be completed in 2016. NIDCD hopes that this investment will translate into less toxic diagnostics and therapies that preserve natural hearing.

NIAMS is the lead NIH Institute for research on a number of autoimmune diseases, such as RA, lupus, scleroderma, psoriasis, vitiligo, alopecia areata, and pemphigus. NIAMS-funded research focuses on enhancing understanding of the genetics and causes of autoimmune diseases and supporting clinical research to improve diagnosis and treatment. For example, in FY 2012, NIAMS continued support for Predictors of Pregnancy Outcome in SLE and Anti-Phospholipid Syndrome, an observational study of 700 pregnant patients, enrolled at nine major clinical centers, designed to determine whether certain proteins that can injure healthy organs can be used to predict poor pregnancy outcome in patients with SLE and anti-phospholipid syndrome, and whether elevated levels of circulating antiangiogenic factors predict pregnancy complications in patients with these disorders. In FY 2012–2013, NIAMS also supported the Childhood Arthritis and Rheumatology Research Alliance, an organization of more than 390 pediatric rheumatologists and researchers who are working together to find treatments for juvenile arthritis and other diseases of the joints, muscles, and bones in children. NIAMS also continued to lead, on behalf of the HHS Secretary, the Lupus Federal Working Group, which provides a forum for its members to learn about lupus research and related activities across the federal government.

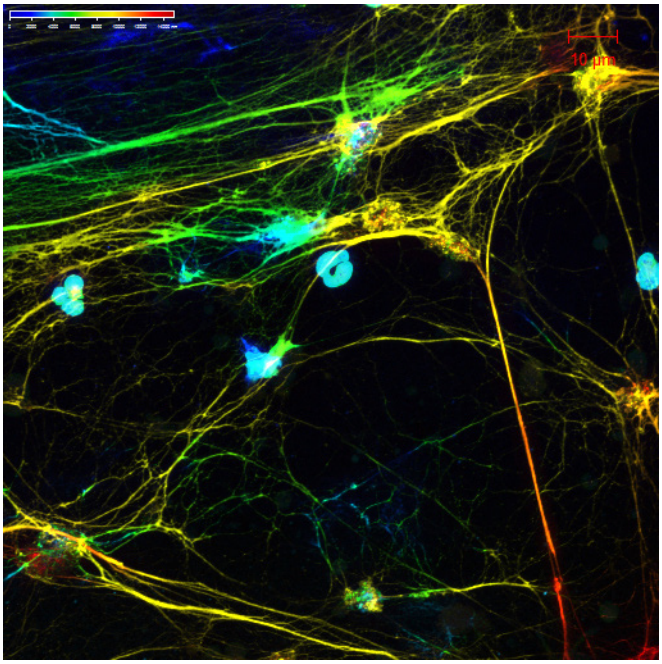


Figure 3-17. *Certain types of the cells, known as low-density granulocytes (LDG), are suspected to have a role in systemic lupus erythematosus (SLE) and other autoimmune diseases. There is evidence that they contribute to organ-damaging inflammation and can form neutrophil extracellular traps (NETs), which may promote autoantibody production. In this image, NET formation in LDGs has been detected by a laser confocal microscope. Understanding how these cells act may give clues to new targets for treatment of diseases like SLE. Credit: Mariana J. Kaplan, M.D., NIAMS.*

In FY 2012, NIAMS-supported researchers reported results from the Atherosclerosis Prevention in Pediatric Lupus Erythematosus study of the potential benefits of statin treatment to slow the progression of atherosclerosis in children with lupus.[643, 644] Statins are used widely in adult populations for the control of atherosclerosis. Lupus in pediatric populations is generally more severe than in adults and is associated with comorbidities, such as CVD, related to premature atherosclerosis. While the results did not demonstrate compelling evidence to support treatment with statins in children and adolescents with lupus, further analyses may identify subgroups of children who may benefit from targeted statin therapy. This finding is important because it lets doctors know that they do not need to prescribe statins for every child with lupus and will therefore spare children the cost and potential side effects of the drug.

In FY 2013, research supported by NIAMS identified 14 genes linked to juvenile idiopathic arthritis, the most common type of arthritis affecting children.[645, 646] In addition to the 14 new genes, the analyses confirmed three

[643] http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2012/statins_atherosclerosis_lupus.asp.
[644] Schanberg LE, et al. *Arthritis Rheum*. 2012;64(1):285–96. PMID: 22031171.
[645] http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2013/jia_genes.asp.
[646] Hinks, A, et al. *Nat Genet*. 2013;45(6):664–9. PMID: 23603761.

previously discovered genes and suggested that another 11 genetic regions might be involved in the disease. The findings are helping researchers to identify novel disease mechanisms that can inform drug design. Also, by comparing genes, scientists hope to further define juvenile idiopathic arthritis subtypes, which could help doctors determine which children are most likely—or unlikely—to respond to a particular treatment.

In research for RA treatment, NIAMS intramural researchers working with NIAMS-funded extramural scientists and other colleagues reported in FY 2013 that taking methotrexate—a commonly prescribed anti-inflammatory medication—might reduce the risk of death among patients with RA.[647, 648] After adjusting for a wide range of patient characteristics that might affect survival, methotrexate use was still associated with a significantly lower risk of death—up to a 70 percent reduction compared with those not taking the drug. The protective effect kicked in after taking methotrexate for more than one year, but it did not increase with longer duration of use. This finding suggests that the drug's benefits are not cumulative over the long term. Rather, the drug likely needs to be taken continuously to maintain its therapeutic value.

NIAMS-funded basic research also contributed to FDA approval of a new treatment for RA in 2012.[649] The drug, tofacitinib, targets a protein discovered at NIH in 1993. Following many years of collaboration between NIH and private industry, tofacitinib became the first drug approved in more than a decade that can be taken as a pill, rather than as an injection, to slow or halt joint damage from RA. It provides an option for adults with moderately to severely active RA who do not respond well to the standard therapy of methotrexate described above.

[647] http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2013/ra_death_risk.asp.
[648] Wasko MCM, et al. *Arthritis Rheum*. 2013;65(2):334–42. PMID: 23044791.
[649] http://www.niams.nih.gov/News_and_Events/Press_Releases/2012/12_4.asp.

Also in FY 2013, a NIAMS-funded study showed that a drug delivery system using nanoparticle technology that allows for better targeting of specific immune cells can potentially improve treatment approaches for SLE.[650, 651] Researchers designed and tested a drug delivery mechanism called a nanogel to administer an immunosuppressant drug used to treat lupus. Compared to conventional administration, the mice receiving the nanogel treatment experienced longer lives (three months longer) and more time before developing kidney damage. The nanogel also provided consistent levels of the drug throughout the body for longer periods of time than the conventional drug, allowing for lower doses. In addition, this new approach does not delete white blood cells, leaving patients less vulnerable to infection, without any evidence of blood, liver, or kidney toxicities.

NIAMS-supported researchers showed in FY 2013 that altering a key protein involved in the development of vitiligo may protect against—or even reverse—the pigmentation loss associated with the skin disorder in mice.[652, 653] Vitiligo is a progressive autoimmune disease in which the skin cells that impart color (melanocytes) are destroyed, resulting in white patches on the face, hands, and other parts of the body. Seventy-six percent of normal pigment returned when the key protein was given to the vitiligo-affected mice, essentially reversing the disease. Although it remains to be seen whether this approach is safe and could have a positive impact on human patients with active disease, the study provides preclinical evidence for a new strategy to reverse the effects of vitiligo.

[650] http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2013/novel_drug_lupus.asp.
[651] Look M, et al. *J Clin Invest*. 2013;123(4):1741–9. PMID: 23454752.
[652] http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2013/vitiligo_protein.asp.
[653] Mosenson JA, et al. *Sci Transl Med*. 2013;5(174):174ra28. PMID: 23447019.

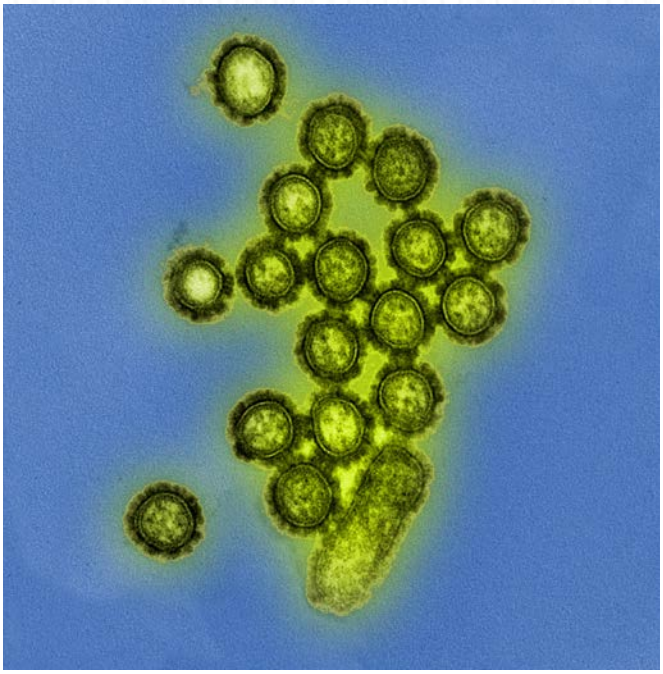


Figure 3-18. *Colorized transmission electron micrograph of H1N1 influenza virus particles. Surface proteins on the virus particles are shown in black. Credit: NIAID.*

Infectious Diseases and Biodefense

Infectious diseases are caused by microbial pathogens and other infectious agents—bacteria, viruses, fungi, protozoa, helminths (worms), and prions—that invade the body and multiply, causing physiological damage and illness. These agents cause a range of diseases—from minor to life-threatening—and can be transmitted in many ways. Influenza and tuberculosis (TB), for example, can be transmitted from person to person through the air; HIV, which causes AIDS, Ebola virus disease, and some forms of viral hepatitis are transmitted through exposure to blood or other body fluids; and malaria is caused by a parasite that is transmitted by an insect "vector," in this case a mosquito.

Threats to public health change continually as new pathogens emerge in nature and as familiar microbes reemerge with new properties or in unusual settings. Public health threats that could cause large-scale disruption and devastation also include the deliberate release of pathogenic agents, such as anthrax or smallpox.

NIH supports and conducts research on hundreds of pathogens and the diseases they cause, including HIV/AIDS, TB, malaria, E. coli, and emerging and re-emerging infectious diseases, such as hemorrhagic fevers caused by Ebola and other viruses, Middle East respiratory syndrome coronavirus (MERS-CoV), chikungunya virus, West Nile virus, Lyme disease, prion diseases, plague and other diseases caused by biodefense pathogens, and influenza.

In 2012, infectious diseases and maternal, neonatal, and nutrition conditions collectively caused approximately 23 percent of all deaths worldwide. Each year, more than 11 million people die from infectious diseases; the vast majority of deaths from infectious diseases occur in low- and middle-income countries (LMIC). The infectious diseases that today cause the greatest number of human deaths worldwide are lower respiratory infections, HIV/AIDS, diarrheal diseases, malaria, and TB.[654] Worldwide, HIV caused 1.5 [1.4–1.7] million deaths in 2013,[655] TB killed 1.5 million in 2013,[656] and lower respiratory infections caused an estimated 3.1 million deaths in 2012.[657] Malaria is a serious problem, especially in Africa, where a child dies every minute from the effects of the disease.[658]

In 2012, 83 percent of deaths in children younger than age 5 were caused by infectious, neonatal, or nutritional conditions. Globally, the top infectious disease causes of death in this age group were pneumonia and diarrheal diseases. In sub-Saharan Africa, malaria caused approximately 15 percent of deaths in children younger than age 5.[659]

The burden of infectious diseases is not evenly shared, even among developing nations. People who live in sub-Saharan Africa are most affected, particularly by HIV/AIDS, which accounts for nearly 70 percent of the global total of new HIV infections. Africa and the most populous countries of Asia harbor the largest number of TB cases. In 2012, the largest number of new TB cases occurred in Asia, accounting for 60 percent of new cases globally.

[654] http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.
[655] http://www.who.int/mediacentre/factsheets/fs360/en/.
[656] http://www.who.int/mediacentre/factsheets/fs104/en/.
[657] http://www.who.int/mediacentre/factsheets/fs310/en/.
[658] http://www.who.int/mediacentre/factsheets/fs094/en/.
[659] http://www.who.int/gho/child_health/mortality/causes/en/.

In the U.S., infectious diseases add significantly to the overall burden of illness. Together, influenza and pneumonia accounted for more than 53,000 deaths in 2010.[660] More than 1.2 million people were living with HIV in the U.S., and each year brings another 50,000 new infections. Unfortunately, almost 13 percent of those people living with HIV are unaware of their infection.[661] An estimated 3.2 million persons in the U.S. have chronic hepatitis C and approximately 800,000 to 1.4 million are affected by chronic hepatitis B.

NIH-wide research on emerging and re-emerging infectious diseases and biodefense includes basic research to understand fundamental mechanisms by which microorganisms cause disease, the host response to pathogens, and mechanisms by which insects and other vectors transmit infectious diseases. This fundamental knowledge base is applied to the development of new and improved medical countermeasures, including diagnostics and therapeutics, as well as vaccines and other preventive measures. NIH conducts and supports clinical research to assess the efficacy and safety of candidate drugs, vaccines, and other products.

Vaccines to prevent infectious diseases are among the most effective and economical measures available to improve human health. Many vaccines include compounds called adjuvants to increase their effectiveness and reduce the number of shots and the amount of immunizing materials needed to produce a protective immune response. In 2013, NIAID IRP began a multi-investigator initiative to identify the key step(s) that regulate the persistence of antibody levels after vaccination and determine how adjuvants elicit the particular events that support this persistence. This information will be used to select or design adjuvants for human use and enhance our ability to produce effective new vaccines against diverse pathogens.

NIH continues to develop a flexible domestic and international infrastructure responsive to newly emerging and re-emerging infectious disease, protecting public health in the U.S. and abroad. Infectious diseases and biodefense are global concerns, and U.S. academic institutions and scientists remain interested in expanding international collaborative research and training. In response to this interest and important scientific opportunities, NIH engages in international research and training partnerships focused on disease detection, prevention, treatment, and control. NIH also supports international programs to foster research and research capacity enhancement in developing countries. Increasingly, these programs involve cooperative funding, which engage NIH foreign counterpart organizations in cost-sharing strategies. Within the U.S., NIH seeks strategic partnerships with other governmental and nongovernmental organizations that are also interested in the scientific opportunities provided by global research.

NIH Funding for Infectious Diseases and Biodefense Research

NIH funding for infectious diseases research was $3,867 million in FY 2012 and $4,887 million in FY 2013.[662] NIH funding for biodefense research was $1,791 million in FY 2012 and $1,692 million in FY 2013.[663]

Major Infectious Diseases

NIH conducts research on hundreds of infectious diseases. Research includes studies of major infectious diseases, such as TB, malaria, and HIV/AIDS, as well as studies to ensure the health of special populations—individuals whose immune systems are compromised, older people, adolescents, young children, pregnant women, and infants. NIH also explores how human behaviors as well as social, cultural, economic, and geographic factors affect disease transmission.

HIV/AIDS

HIV/AIDS remains a leading cause of death worldwide, especially in sub-Saharan Africa. New infections continue to impede efforts to curtail the epidemic domestically as well as internationally. Furthermore, even though the advent of antiretroviral therapy (ART) has significantly improved the longevity of HIV-infected individuals, AIDS-related coinfections remain a significant cause of morbidity and premature

[660] http://www.cdc.gov/nchs/fastats/deaths.htm.
[661] http://www.cdc.gov/hiv/statistics/basics/ataglance.html.
[662] http://report.nih.gov/categorical_spending.aspx.
[663] Reporting for this category does not follow the standard RCDC process. The total amount reported is consistent with reporting requirements for this category to the U.S. Office of Management & Budget (OMB). The project listing does not include non-project or other support costs associated with the annual total for this category. For more information, see http://www.niaid.nih.gov/topics/biodefenserelated/pages/default.aspx.

mortality in LMICs. Without an effective preventive vaccine or improved treatments that allow HIV-infected individuals to discontinue ART (i.e., a functional cure), the economic burden of HIV/AIDS will increase as new infections and use of ART continue to rise. NIH is committed to developing new prevention methods, including a vaccine, and cure and treatment strategies in the hopes of achieving an "AIDS-free generation" through the combined use of prevention and treatment tools.

To address the HIV/AIDS pandemic, NIH conducts and supports a comprehensive program of basic, clinical, translational, and behavioral research on HIV infection and its associated coinfections, malignancies, and other complications. All NIH ICs support HIV/AIDS-related research activities, consistent with their individual missions. OAR coordinates all NIH-funded HIV/AIDS research and develops an annual *Trans-NIH Strategic Plan for HIV-Related Research*. The OAR planning process involves government and nongovernment experts and representatives from community constituency groups to identify overarching AIDS research priorities and specific research objectives. The annual trans-NIH AIDS research budget is tied explicitly to the objectives of the *Strategic Plan*. This process reduces redundancy, promotes harmonization, and assures cross-Institute collaboration to conduct and support research in domestic and international settings. OAR identifies emerging scientific opportunities and public health challenges that require focused attention, manages and facilitates multi-Institute and trans-Institute activities to address those needs, fosters research by designating funds and supplements to jump-start or pilot program areas, sponsors reviews or evaluations of research program areas, and facilitates international AIDS research and training.

NIAID HIV/AIDS Clinical Trials Networks (comprising leadership groups and clinical trial sites) provide a domestic and international research infrastructure for conducting clinical trials on all aspects of HIV/AIDS. These networks provide multiple opportunities for cross-NIH collaborations, with NIMH, NICHD, NIDA, NINDS, NCI, NIDCR, and OAR providing additional funding for specific networks or studies. In 2013, NIAID restructured its HIV/AIDS Clinical Trials Networks[664] to create a more efficient and cost-effective

[664] http://www.niaid.nih.gov/news/newsreleases/2013/pages/clinical-trials-network.aspx.

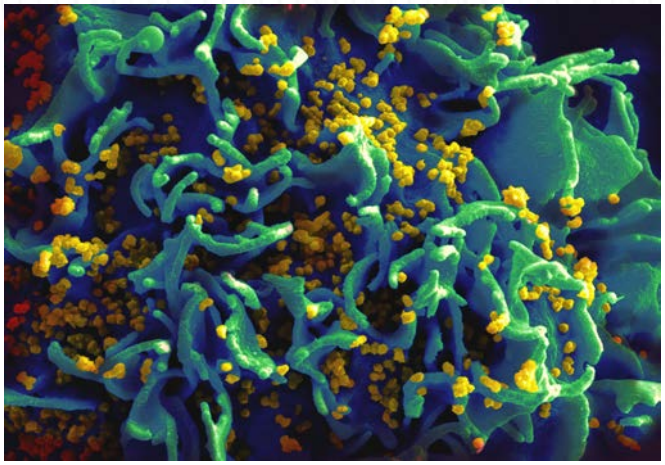


Figure 3-19. *Scanning electron micrograph of HIV particles infecting a human T cell. Credit: NIAID.*

infrastructure capable of advancing high-priority research on HIV/AIDS and HIV/AIDS-associated infectious diseases and comorbidities (e.g., TB, hepatitis) as well as a network dedicated to antibacterial resistance.

The best long-term hope for controlling the HIV/AIDS pandemic, and one of the highest research priorities of NIH, is the development of a safe and effective HIV vaccine that can prevent HIV infection either by itself or in combination with other prevention strategies. NIH is building on the results of the RV144 vaccine trial, the first HIV vaccine trial to demonstrate a modest reduction in the risk of HIV transmission, through the Pox-Protein Public-Private Partnership (P5) initiative. The P5 is an international collaboration among NIAID, the Bill & Melinda Gates Foundation, HIV Vaccine Trials Network, Military HIV Research Program, Sanofi Pasteur, Novartis, EuroVacc, and the Republic of South Africa.

NIH-led scientists have discovered and characterized human antibodies that can block a wide range of HIV strains from infecting human cells in the laboratory. Understanding how these broadly neutralizing antibodies neutralize HIV could serve as the foundation for the rational design of future vaccine candidates. The NIAID Vaccine Research Center (VRC) also has increased its efforts on isolating broadly neutralizing monoclonal antibodies; identifying and characterizing the structures of vulnerable viral surfaces; and designing immunogens to elicit potent, broadly neutralizing antibodies against HIV. This structural biology work

continues to drive the VRC's approach of targeted design of active vaccine immunogens. In 2013, testing and evaluation began on one broadly neutralizing antibody, called VRC01, in Phase I clinical trials in infected and uninfected adults.

Research is ongoing on the role of cellular immunity in active immunization, its influence on humoral immunity, and the ability of white blood cells called CD8 cells to prevent infection. The VRC also is developing second-generation antibody products to test the concept of passive immunization in adults, using modifications intended to reduce the requirement for product while retaining the ability of the antibody to confer protection against infection by diverse strains.

In 2013, NIAID hosted a *Mini-Summit on Adenovirus Platforms for HIV Vaccines*,[665] which brought together experts in all aspects of HIV vaccinology. The attendees discussed the impact of a type of vaccine known as rAd5 HIV vaccines on HIV acquisition, mechanisms, and how current data from several clinical studies should inform future trials. These vaccines are based on a weakened adenovirus type 5, a common virus that normally causes upper respiratory infections, such as the common cold, but that has been altered to render it unable to replicate. Data presented at the summit suggested that rAd5-HIV vaccines do not prevent infections and may increase the risk of HIV infection. As a result, NIAID will no longer evaluate this type of vaccine but will continue to support research on other rAd-HIV vaccines. In 2012, NIAID established the new Centers for HIV/AIDS Vaccine Immunology & Immunogen Discovery. This research consortium is designed to accelerate HIV vaccine development by supporting multidisciplinary research into immune responses that prevent or contain HIV infection and by generating model vaccine components that can induce these protective immune responses.

Recent studies have demonstrated that HIV treatment can prevent HIV transmission, but additional research is needed to optimize (ART) at the population level. In 2013, an NIMH-funded trial identified a novel evidence-based program for improving ARV medication adherence among HIV/AIDS patients. The program, titled *Managed Problem Solving*, paired problem-solving adherence counseling with medication adherence monitoring through an electronic pill container. Participants in the intervention arm demonstrated significantly higher ARV adherence and marginally improved viral load.[666] In another example, the TLC-Plus study, which provides immediate ARV treatment to those that test positive for HIV, is evaluating the feasibility of an enhanced community-level test, link to care, plus treatment strategy. This proof-of-concept study will provide key information that could guide the design of a future large, randomized, community-level clinical trial and the implementation of this strategy in the U.S. and around the world. In addition, in 2013 NIH launched a study in South Africa and Zambia that will assess whether house-to-house voluntary HIV testing and prompt treatment of HIV infection, along with other proven HIV prevention measures, can reduce substantially the number of new HIV infections across communities.

Another key strategy in HIV prevention is the use of ART to prevent mother-to-child transmission (MTCT). NICHD, in collaboration with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), initiated research to evaluate the safety and effectiveness of the WHO-recommended triple ART drug strategies for prevention of mother-to-child transmission, particularly the recommendation for initiating life-long therapy for all pregnant women. Nine investigators in six African countries will address critical research areas, including the evolution of birth outcomes with in utero ART exposure (a collaborative project with CDC), innovative methods to promote maternal ART adherence, and retention of mothers and infants in care, as well as population-based studies to evaluate the long-term effectiveness of the WHO recommendations. NIH also continues to support the Promoting Maternal-Infant Survival Everywhere study, a Phase III clinical trial designed to determine how best to reduce the risk of HIV transmission from infected pregnant women to their infants during pregnancy and breastfeeding while preserving the health of these children and mothers.

HIV infection is associated with chronic activation of the immune system. One cause of this chronic immune activation is increased microbial translocation from the intestine into the bloodstream due to damage to the GI tract. NIAID IRP scientists found significant improvement of

[665] http://www.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/Pages/adenovirusPlatforms.aspx.

[666] Gross R, et al. *JAMA Intern Med*. 2013;173(4):300–6. PMID: 23358784.

the GI tract immune system after treatment with ART and supplemental probiotics in Asian macaques infected with simian immunodeficiency virus—the monkey version of HIV.[667] If ongoing work extends this finding to HIV infection, probiotic/prebiotic treatment may be a useful addition to ART in HIV-infected individuals to mitigate residual GI inflammation and damage and thereby improve prognosis.

NIH is focused on developing strategies that could result in complete eradication or long-term HIV remission so that ART is no longer necessary for HIV-infected individuals. The "Mississippi baby," an HIV-infected infant for whom ART was initiated within 30 hours of birth, with subsequent interruption of therapy by her parents at 18 months, had an unprecedented 27-month sustained remission of viral replication after therapy. While not completely successful, early ART appeared to considerably limit the HIV reservoir and averted the need for antiretroviral medication for a prolonged period. Development of the latent reservoir among perinatally infected infants may differ from reservoir establishment in adults, given the immature and developing nature of the immune system in the fetus and infant. Additionally, given the ability to rapidly diagnose infants at birth, initiation of ART very near the time of infection is more possible in infants than in adults. NICHD, NIAID, and NIMH are funding research to understand more about the latent reservoir establishment in HIV-infected infants and to determine if the period of sustained remission in the absence of therapy can be prolonged even further.

The NIAID IRP continues to seek new methods to disrupt HIV's lifecycle and prevent chronic infection. In 2012, NIAID scientists reported that the chemokine CXCL4/PF-4, an abundant platelet-derived protein, was a broad-spectrum HIV inhibitor that acts through an unconventional antiviral mechanism. Investigations are underway to define a potential role for this inhibitor in HIV treatment and prevention.[668]

In 2012–2013, NIH research made significant advances in understanding the manner in which HIV-related neurological disorders develop. NIMH-funded investigators have studied the earliest events in the CNS during HIV infection, and they found that on average, the degree of HIV-related RNA maturation in brain plasma was higher than that in the cerebrospinal fluid. These findings provide evidence for the early establishment of HIV reservoirs in the brain.[669] Another NIMH-funded team developed a small-molecule drug candidate that has shown promise in neuroprotective and anti-inflammatory models of HIV-associated neurocognitive disorders.[670] Researchers are continuing to investigate the ability of this drug candidate to modulate gene networks involved in the manner in which these disorders develop.

Virus-associated oral infections and cancers remain a significant oral health issue, especially for immune-compromised individuals, such as those with HIV/AIDS. NIDCR supports research on the pathogenesis and prevention of HIV-related oral complications and cancers due to infections from HIV and oral opportunistic viruses, bacteria, and fungi. NIDCR also funds research to develop safe and effective preventive strategies to block HIV and oral pathogen infections. NIDCR continues to recognize the importance of clinical research studies in children, adolescents, and adults to develop a comprehensive approach to improve the clinical diagnosis, treatment, and management of comorbidities and malignancies of AIDS-related oral complications. NIDCR-sponsored clinical studies are conducted through the Oral HIV/AIDS Research Alliance in collaboration with NIAID and the Pediatric HIV/AIDS Cohort Study[671] in collaboration with NICHD.

Another important area of prevention research that will particularly benefit women is the development and testing of microbicides. These products can be used alone or in combination with other strategies to prevent transmission of HIV and other sexually transmitted infections. Microbicides represent a promising approach to primary HIV prevention. NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of microbicide candidates. In 2012, NIH launched a new study to evaluate the effectiveness and extended safety of a vaginal ring containing an experimental antiretroviral drug to prevent HIV infection in women.[672]

[667] Klatt NR, et al. *J Clin Invest*. 2013;123:903–7. PMID: 23321668.
[668] Auerbach DJ, et al. *Proc Natl Acad Sci U S A*. 2012;109:9569–74. PMID: 22645343.
[669] Valcour V, et al. *J Infect Dis*. 2012;206(2):275–82. PMID: 22551810.
[670] Marker DF, et al. *J Neurosci*. 2013;33(24):9998–10010. PMID: 23761895.
[671] https://phacs.nichdclinicalstudies.org/default.asp.
[672] http://www.niaid.nih.gov/news/newsreleases/2012/Pages/ASPIRE.aspx.

Adolescents are one of the largest growing risk groups for HIV infection. There is a growing domestic and global epidemic in youth: worldwide, an estimated 5 million young people ages 15–24 live with HIV infection and, in the U.S., new HIV infections among youth comprise more than 25 percent of all new infections. WHO estimates that HIV/AIDS is currently the second leading cause of death among adolescents globally. The NICHD-, NIDA-, and NIMH-funded Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) is a multicenter basic science and clinical research network, with multiple clinical sites across the U.S., that focuses on the prevention, treatment and management of HIV infection and its complications among youth ages 12–24. ATN conducts studies to evaluate promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in adolescents with HIV infection and those at risk of HIV infection. A strong multiagency collaboration exists among ATN, NICHD, CDC, and HRSA to improve the identification, linkage, and engagement to care of minority youth with undiagnosed HIV infection in the U.S. Globally, despite substantial HIV incidence in youth, access to, and uptake of, HIV testing, counseling, and linkage to care is significantly lower for youth than for adults. In collaboration with UNICEF, NICHD, and partner ICs, ATN will initiate research to evaluate the unique barriers or facilitators for testing and linkage to care and identify interventions to improve these among youth in resource-limited countries.

Moving forward, NIH is supporting HIV/AIDS research to develop better, less toxic treatments and investigate how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors interact to affect treatment success or failure and disease progression. Studies will continue to address the increased incidence of malignancies, neurologic issues, cardiovascular and metabolic complications, and premature aging associated with long-term HIV disease and ART. Translational research is focusing on the feasibility, effectiveness, and sustainability required to scale up interventions from a structured behavioral or clinical study to a broader real-world setting.

Malaria

Malaria, caused by several parasites of the genus *Plasmodium* and transmitted by mosquitoes, continues to be the most important parasitic disease in terms of annual mortality. About 3.4 billion people—half of the world's population—are at risk of contracting malaria. Worldwide, an estimated 207 million clinical cases of malaria occurred in 2012.[673] People living in the poorest countries are the most vulnerable to the disease. It is an especially serious problem in Africa. In 2012, malaria killed an estimated 482,000 children younger than age 5. The magnitude of worldwide disease burden and the existing barriers to controlling infection, disease, and transmission require multiple approaches for the prevention and treatment of malaria.

NIAID supports research that provides the knowledge and tools needed to make real improvements in disease prevention, control, and treatment. Several Global Health Initiative target areas, including malaria, are key foci of the NIAID research program, which has invested heavily in translational research to support the development of vaccines, therapeutics, and diagnostics.

NIAID-supported investigators and NIAID intramural scientists are also working to develop a vaccine against malaria. NIAID provides product development support for six malaria vaccine candidates currently in clinical trials. With funding by the PATH Malaria Vaccine Initiative, a consortium of laboratories led by the NIAID IRP is evaluating novel antigens that induce anti-infection immunity in rodent models. It is hoped that these antigens will show promise as future human vaccine candidates. An effective malaria vaccine would produce large economic benefits by reducing health care costs and helping to stabilize the economies of countries where malaria is endemic. A Phase I clinical trial by NIAID researchers and their collaborators showed that an investigational malaria vaccine known as the PfSPZ vaccine is safe, generates an immune system response, and protects against malaria infection in healthy adults. The vaccine, which was developed by scientists at Sanaria Inc., is composed of live, but weakened, sporozoites of the species *Plasmodium falciparum*, the most deadly of the malaria-causing parasites. A number of follow-up studies

[673] http://www.who.int/malaria/media/world_malaria_report_2013/en/.

are planned, including research to evaluate the vaccine's different dose schedules, possible protection against other *Plasmodium* strains, and the durability of protection.

As part of its commitment to the Global Health Initiative, NIAID partners with various organizations, such as USAID, WHO, the Commission of the European Community, the European-Developing Countries Clinical Trials Partnership, the European Vaccine Initiative, the Wellcome Trust, the Bill & Melinda Gates Foundation, the PATH Malaria Vaccine Initiative, the Medicines for Malaria Venture, and the Multilateral Initiative on Malaria. In addition, NIAID supports the *Global Malaria Action Plan*,[674] an international framework for coordinated action designed to control, eliminate, and eradicate malaria that provides access for U.S. and international scientists to multiple research resources as well as training for new investigators.

Because the risk of childhood malaria is related to exposure before birth to the malaria parasite through infected mothers, NIAID scientists recently initiated a program on malaria disease development in pregnant women and young children that could yield new preventive measures and treatments for these most vulnerable groups. NICHD is also funding investigators to determine the optimal antimalarial drug prophylaxis interventions to prevent malaria among HIV-infected and uninfected pregnant women and their infants and evaluating interactions between anti-malarial and anti-HIV drugs in HIV-infected women and children.

The NIAID IRP also has been focusing on key factors in mosquito-parasite interactions to understand mosquito immune defenses and malaria parasite coping mechanisms. In 2013, NIAID scientists reported finding a gene that allows *P. falciparum* to efficiently infect mosquitoes and be transmitted to people. The parasite's ability to evade the mosquito immune system may contribute to the high rate of malaria transmission in some areas where the disease is prevalent. The scientists are investigating whether antibodies against the gene can block its function and allow the mosquito immune system to recognize and eliminate malaria-causing parasites. This work is building toward a future where transmission of the malaria parasite can be controlled through strategies that exploit the mosquito's defense mechanisms.[675]

[674] http://www.rollbackmalaria.org/microsites/gmap/.
[675] http://www.niaid.nih.gov/topics/Malaria/research/Pages/geneParasiteMosquito.aspx.

NIAID researchers, working with French and Cambodian colleagues in Cambodia, have developed two tests that can detect malaria parasite resistance to artemisinin, the key drug used to treat malaria. One test provides results in 72 hours and can predict whether a patient has slow-clearing, drug-resistant parasites, which could be useful for surveillance studies to monitor the emergence or spread of artemisinin-resistant malaria parasites. The second test will likely be most useful in future studies designed to elucidate the molecular basis of artemisinin resistance and to screen new malaria drugs. Both tests are faster and less costly than current tests of drug responsiveness.[676]

In 2010, researchers described a chemical that rids mice of malaria-causing parasites after a single oral dose, raising hopes that the chemical may eventually become a new malaria drug. The compound, KAE609, was identified by an international team of NIAID-funded extramural and intramural investigators following an analysis of more than 12,000 chemicals using a robotic screening technique customized to detect compounds active against the most deadly malaria parasite. A clinical trial to assess KAE609's activity in people began in Thailand in 2012. Research on KAE609 is a continuing collaboration among NIH-funded scientists, the pharmaceutical company Novartis, and the nonprofit Medicines for Malaria Venture.

Tuberculosis

TB, an infection caused by a bacterium called *Mycobacterium tuberculosis* (Mtb) that most often affects the lungs, remains a major cause of disability and death worldwide. In 2013, 9 million people around the world became sick with TB and nearly 1.5 million people died from the disease.[650] The continued increase of drug-resistant TB poses a major global health threat. NIAID has supported a long-standing effort to understand the various stages of TB; how Mtb causes the disease; how drug resistance emerges; and what approaches and tools are needed to manage, prevent, and combat TB.

WHO estimates that in 2012, 450,000 persons developed multidrug-resistant (MDR) TB, which led to approximately 170,000 deaths, and that most cases of MDR TB occur in eastern Europe and central Asia. In response to this growing

[676] http://www.niaid.nih.gov/news/newsreleases/2013/Pages/DrugResistantMalariaTests.aspx.

international public health challenge, NIAID expanded its TB research to help combat drug-resistant TB. For example, NIAID established research cohorts in India to identify biological markers of infection and disease for TB in the presence and absence of coinfections and comorbidities that contribute to India's TB epidemic. NICHD is providing additional funding to these research cohorts to include studies on TB in pregnant women and children.

At least one-third of the 35.3 million people living with HIV worldwide are thought to be infected with Mtb, and in 2012, 1.1 million TB patients also were coinfected with HIV. Among people with HIV/AIDS, TB is a major coinfection and the leading cause of death, responsible for killing approximately 320,000 HIV-infected individuals in 2012. In FY 2013, NIAID restructured the HIV/AIDS Clinical Trials Networks[677] and expanded their capabilities so that they can address key scientific questions about the high rate of TB coinfection in HIV-infected individuals and also contribute to studies of TB in the absence of HIV coinfection to provide data critical for the improved management of TB in all affected persons. NIAID continues to collaborate with the global TB research community, other funders, and the U.S. Federal Tuberculosis Task Force to coordinate resources, leverage support for fundamental and translational studies, and assure the realization of opportunities for contributing to the development of new health care interventions.

Collaborations among the NIAID IRP, NIH, the Bill & Melinda Gates Foundation, and many other private and public partners are investigating TB drug development, the development of animal models for TB, biomarkers of responses to therapy, and the biology of latency. Through its Genomics Centers and its Bioinformatics Resource Centers and Databases, NIAID initiated collaborations with research partners in TB endemic countries. These studies are designed to provide insight into the genetic diversity of Mtb and catalog genetic markers that underlie resistance to first- and second-line drugs. Genomics data and analysis from these studies will be made publicly available through NLM- and NIAID-funded databases and are expected to inform the development of molecular diagnostics for drug resistance testing, provide new targets for drug development, and contribute to the understanding of the differences and commonalities of TB epidemiology in high-burden countries. In addition, NIAID established the Tuberculosis Diagnostics Research Forum to facilitate communication, coordination, and collaboration among funding, research, and implementing organizations to accelerate research translation and development and optimize the use of available funds for this research. NIAID's product development infrastructure, through its preclinical and clinical services programs, continues to contribute to the advancement of many drugs, vaccines, and diagnostics that are part of the global TB product pipeline. One-third of the current clinical drug candidates, close to half of the clinical vaccine candidates, and many diagnostic tests that are in development have been supported through NIAID resources during their preclinical/clinical development stages. Preclinical and clinical studies on new TB drugs and vaccines are benefiting from a variety of advances including an improved understanding of host immune responses during infection and disease; innovative new immune assays to measure the effects of vaccines; and new drug targets identified through systems biology approaches that target key metabolic aspects of Mtb. NIAID is also developing new drug formulations to be used as adjunctive therapy for MDR TB.

The strategic efforts of the NIAID TB program, in collaboration with other NIAID and NIH programs, contribute to all aspects of TB research—from developing biomarkers and rapid, sensitive diagnostics to stimulating the development of preventive measures, such as vaccines and treatments for latent (dormant) Mtb infections, to accelerating the development of new anti-infective and adjunct therapeutic approaches to improve care of TB patients.

Some recent activities in TB research include:

- Drug resistance development in TB and other infectious diseases is often a result of inadequate drug levels at the site of infection or suboptimal doses of drugs that are given in combinations. To better understand the interplay of drug levels in humans or animal models with the dynamics of bacterial growth, NIAID is supporting pharmacologically based studies to improve treatment and prevention of drug resistance.

[677] http://www.niaid.nih.gov/news/newsreleases/2013/pages/clinical-trials-network.aspx.

- The biochemistry and life cycle of Mtb, especially in the context of the host immune response, can provide critical information needed to identify points of vulnerability against which novel drugs or vaccines can be directed. These systems biology projects contribute integrated data across complex biological processes and are shedding light on the complex nature of this infectious disease.
- NIAID's preclinical in vitro and in vivo services are evaluating the ability of selected small molecule chemicals to interfere with Mtb viability and growth in the test tube and in animals for the purpose of developing drug candidates with novel mechanisms of action that can be used against drug-sensitive and drug-resistant bacteria alike. These services contribute to, and complement, research activities supported at academic, public/private, and for-profit organizations and are an important resource to assure that the product pipeline for TB remains filled.
- Several Phase I/II clinical trials are investigating the safety and preliminary efficacy of new and existing clinical TB drug candidates. In addition, a Phase III ReMOX trial of two 4-month combinations, including moxifloxacin for TB treatment versus the standard 6-month regimen, is ongoing in collaboration with the Global Alliance for TB Drug Development.
- Several early-phase and late-phase clinical trials are ongoing to evaluate therapies to prevent or treat TB coinfection in people living with HIV, including children. Also ongoing is an early-phase clinical study to evaluate the safety of an experimental TB vaccine given as a boost to the existing BCG (bacille Calmette-Guerin) TB vaccine in HIV-uninfected infants.
- NIAID's vaccine-testing services continue to assess candidate vaccines, adjuvants, and immune stimulants and contribute to new experimental vaccines that may have the potential to protect persons already infected with Mtb.
- NIAID IRP investigators and colleagues from Yonsei University in South Korea led a study of the safety and efficacy of linezolid for the treatment of extensively drug-resistant (XDR) TB. The results suggest that linezolid may become an important therapeutic option for XDR-TB cases in the future. It also may form part of a regimen to treat MDR TB in periods shorter than the two years of therapy that is now standard for such patients. Additional clinical trials are needed to identify a dosage that is sufficiently potent, yet does not cause significant adverse events.[678]
- To identify novel drugs for the treatment of TB, the NIAID IRP leads a consortium of investigators funded by the Bill & Melinda Gates Foundation (with co-funding from the South African Medical Research Council) that conducts whole-cell screening.
- NICHD-funded researchers are evaluating the effect of TB and its treatment in HIV-infected pregnant women and their infants. In separate studies, researchers also are assessing the extent and timing of the suppression of Th1 cytokine production in response to TB-specific antigens and how HIV affects this suppression in pregnant women; describing the cellular mechanism underlying this suppression; and using cytokine/RNA expression profiles to identify a biosignature associated with progression to active TB. Finally, given the lack of data on appropriate dosing of most anti-TB drugs in children, NICHD-funded investigators are evaluating the pharmacokinetics of first- and second-line anti-TB drugs in HIV-infected and uninfected children.
- In line with NIH's global health policy objectives, NLM is leveraging intramural expertise in image processing to create an automated system to screen chest X-rays from HIV-positive patients in rural Kenya for TB and other pulmonary diseases. This system will alleviate the shortage of radiological services in under-resourced areas.[679]

Viral Hepatitis

Five different viruses—hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV)—are known to cause liver disease in humans. All of them can cause acute hepatitis, whereas HBV, HCV, and HDV can also lead to a persistent infection and chronic hepatitis. (Additional information on viral hepatitis is included in the "Digestive Diseases" subsection of the "Chronic Diseases and Organ Systems" section in this chapter.) Collectively, viral hepatitis is the

[678] http://www.niaid.nih.gov/news/newsreleases/2012/Pages/xdrTB.aspx.
[679] http://lhncbc.nlm.nih.gov/project/computer-aided-tb-screening-chest-x-rays.

most common cause of acute and chronic liver disease in the U.S. and worldwide. In the U.S., chronic hepatitis B affects an estimated 700,000–1.4 million people, and chronic hepatitis C affects an estimated 2.7 million–3.9 million people.[680] Furthermore, these diseases are often asymptomatic for many years after the initial infection until signs of cirrhosis or liver cancer develop, which may require liver transplantation.

Hepatitis B Virus

NIDDK supports several research programs related to viral hepatitis, including the Hepatitis B Research Network,[681] established in 2008 to advance understanding of the disease processes and natural history of chronic hepatitis B, as well as develop effective approaches to treatment with currently available therapies. The Network brings together clinical centers from throughout the U.S. and Canada. This multicenter Network is enrolling both adults and children with hepatitis B in multiple clinical trials.

Recent advances include a study supported by NIDDK showing how an immune cell called the natural killer T (NKT) cell mounts an early defense against HBV by sensing modified fat molecules produced by infected liver cells. These findings suggest that natural killer T cells contribute to early immunity against, and clearance of, HBV by alerting the immune system to the viral intruder. This research points to potential approaches to preventing and treating chronic HBV infection through targeting these cells.[682]

In addition, NICHD and CDC co-funded a study to evaluate whether the addition of the use of the anti-HBV drug tenofovir in late pregnancy and immediately postpartum can reduce the risk of HBV mother–to-child transmission in high-risk HBV-infected e-antigen–positive pregnant women. This approach is similar to the approach used for the prevention of HIV mother-to-child transmission. Even with appropriate administration of infant prophylaxis (preventative therapy) with HBV immune globulin and vaccine, mother-to-child HBV transmission is as high as 15 percent; among infants whose mothers have high HBV DNA levels, transmission rates of 39 percent or higher have been noted.[683]

NIAID also supports work in this area. HBV animal model contracts are supporting work in multiple therapeutic areas, including novel antivirals, therapeutic vaccines, Toll-like receptor agonists, immunomodulators, interferon inducers, and new adjuvants. Researchers at Utah State University test drugs against HBV in the HBV transgenic mouse model, and researchers at Georgetown University screen therapeutics in a disease-producing woodchuck infection model.

Hepatitis C Virus

NIAID research is advancing or has helped to advance the development of new therapeutic agents for HCV and adjunct treatments to increase the response rate to a combination treatment (pegylated interferon and ribavirin) for HIV–HCV coinfected patients.

NIAID is also funding research to study a T-cell–based viral-vectored vaccine approach in a Phase II clinical trial that began in 2012 and is expected to be completed in 2016. The trial will test whether this vaccine can prevent the development of chronic HCV infection. The Phase I studies[684] have already shown this vaccine is safe and induces strong T-cell immune responses in healthy humans.

NIDDK funds follow-up and ancillary studies of completed clinical trials on hepatitis C. For example, a clinical trial conducted at seven U.S. liver transplant centers in NIDDK's Adult-to-Adult Living Donor Liver Transplantation Cohort Study showed that pretreatment of HCV-infected patients using antiviral therapy with pegylated interferon and ribavirin to suppress the viral infection can prevent recurrence of the infection once the patients receive a transplanted liver from a healthy donor.[685] This study provides clinical evidence that sustained HCV eradication with antiviral therapy before liver transplant virtually eliminates hepatitis C recurrence post-transplant.[686] In addition, a multicenter clinical trial co-sponsored by NIDDK and NCCAM found that a popular herbal product derived from the milk thistle plant called

[680] http://www.cdc.gov/hepatitis/Statistics/index.htm.
[681] http://www.hepbnet.org/.
[682] Zeissig S, et al. *Nat Med*. 2012;18(7):1060–8. PMID: 22706385.
[683] Kourtis AP, et al. *N Engl J Med*. 2012;366:1749–52. PMID: 22571198.
[684] Barnes E, et al. *Sci Transl Med*. 2012;4(115):115ra1. PMID: 22218690.
[685] Everson GT, et al. *Hepatology*. 2013;57(5):1752–62. PMID: 22821361.
[686] Since the time of this study, results of which were published in 2013, this form of antiviral therapy is no longer a first-line treatment for chronic hepatitis C, having been replaced by the more effective, direct-acting antivirals approved in 2014. However, this finding remains relevant in the context of current treatment approaches.

silymarin did not reduce liver disease in those individuals whose chronic hepatitis C did not respond to traditional antiviral therapy.[687]

A collaborative team of NIDDK and NCI intramural scientists discovered a novel interferon gene, *Interferon Lambda 4*, that codes for a variant protein. Expression of this variant protein is closely associated with clearance of HCV and may be clinically useful in the future, both in predicting treatment responses to HCV infection and as a novel therapeutic agent to help clear the virus and prevent progression to cirrhosis and hepatocellular carcinoma.[688]

In 2012, NIAID IRP researchers identified several factors in people infected with HCV that may predict whether the unusually rapid progression of disease from initial infection to severe liver conditions, such as cirrhosis, will occur. Knowing whether a patient's condition is likely to deteriorate quickly could help physicians decide on the best course of treatment.[689]

NIAID IRP investigators and their colleagues completed the first interferon-free HCV treatment study in the U.S., using sofosbuvir (an HCV polymerase inhibitor) and ribavirin to treat HCV genotype 1 infection. The study population had a higher prevalence of unfavorable predictors of treatment response, including Black race and body mass index greater than 30, than participants in previous studies of two other direct-acting antiviral drugs. The 68 percent overall sustained virologic response rate achieved in participants who received sofosbuvir in combination with weight-based doses of ribavirin in the study is encouraging and provides important information regarding the expected treatment responses in a population representative of the U.S. epidemic.[690]

[687] Fried MW, et al. *JAMA*. 2012;308(3):274–82. PMID: 22797645.
[688] Prokunina-Olsson L, et al. *Nat Genet*. 2013;45(2):164–71. PMID: 23291588.
[689] Farci P, et al. *Proc Natl Acad Sci U S A.* 2012;109(36):14562–7. PMID: 22829669.
[690] Osinusi A, et al. *JAMA*. 2013;310(8):804–11. PMID: 23982366.

Emerging Infectious Diseases and Biodefense (including seasonal and pandemic influenza)

NIH is the lead agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. Recognizing the potential for deliberate use of microorganisms as biological weapons, and the fact that previously controlled microorganisms can re-emerge with new properties (such as drug resistance) or in new settings, NIAID has integrated its biodefense research into the Institute's larger emerging and re-emerging infectious diseases portfolio. This research provides the foundation for developing medical products and strategies to diagnose, treat, and prevent a wide range of infectious diseases, whether those diseases emerge naturally or are deliberately introduced into a population through an act of bioterrorism. No matter what the source of the infectious threat, the research approach is the same: (1) understand the infectious agent and how it causes disease and (2) develop tools to diagnose, treat, and prevent illness caused by that microbe or toxin. The overall goal of research on biodefense and emerging and re-emerging infectious diseases is to develop the knowledge and tools to respond quickly and effectively as public health threats emerge, whether they occur naturally or deliberately.

The NIH biodefense research program has achieved major successes in the development of countermeasures against significant bioterror threats. Some countermeasures are stockpiled or available for emergency use; others in the development pipeline have been transferred to the HHS Biomedical Advanced Research and Development Authority (BARDA) for advanced development. Candidates that have been transitioned from NIAID to BARDA include a broad-spectrum antiviral drug that potentially can be used to treat DNA viruses such as smallpox; vaccines against smallpox and anthrax; and several therapeutics for anthrax, smallpox, and pandemic influenza.

NIAID continues to support the development of medical countermeasures against pathogens and diseases such as anthrax, Ebola, Marburg, MERS-CoV, botulism, and

pandemic influenza, many of which pose potential threats to the U. S. and international communities. Over time, NIH's biodefense research efforts have shifted away from a "one bug–one drug" single-pathogen–focused approach toward a more flexible, broad-spectrum strategy that is applicable to all infectious diseases. In FY 2012, NIAID awarded several contracts to support the development of such broad-spectrum therapies, which can improve preparedness for all infectious threats, whether they occur naturally or are deliberately introduced.

Researchers have made advances in developing countermeasures to numerous disease-causing organisms. For example:

- *Ebola.* Ebola virus produces viral hemorrhagic fever with lethal results in the vast majority of infected individuals. No vaccines or treatments are yet approved for Ebola virus. Scientists at NIAID are evaluating several Ebola vaccines for use in Phase I human clinical trials toward the ultimate goal of developing potential fast-acting vaccines to contain outbreaks of Ebola, whether arising from natural infection or bioterrorism. In addition, NIAID-supported scientists are developing multiple Ebola therapeutics. One therapeutic, MB-003 monoclonal antibody cocktail protects nonhuman primates when administered within five days of exposure to Ebola virus.
- *West Nile Virus.* A live-attenuated West Nile virus (WNV) vaccine developed by NIAID scientists was found to be safe, well tolerated, and able to induce a potent, durable WNV antibody response in healthy adult volunteers. Importantly, neurovirulence and neuropathogenesis studies of this vaccine in rhesus monkeys support further large-scale clinical trials in humans, including older individuals, a group at risk for severe WNV disease.[691]
- *Anthrax.* BioThrax® vaccine has been licensed since 1970 for active immunization for the prevention of disease against all forms of anthrax. However, the primary interest of the U.S. government is to use the vaccine in combination with approved antibiotics in a post-exposure prophylaxis situation, and the sponsor has been pursuing this indication with the U.S. government's support for a three-dose regimen given at zero, two, and four weeks. Through NIAID support, the anthrax vaccine adsorbed was shown to protect animals against an anthrax spore challenge two weeks after completing a two-dose schedule given at zero and two weeks. An interagency group (comprising NIAID, CDC, BARDA, and FDA) is reviewing the data to determine whether they support pursuing a reduction in the current antibiotic regimen of 60 days following exposure to anthrax when also having received two doses of BioThrax.
- *Botulism.* NIAID has supported the development of XOMA 3AB, a monoclonal antibody designed for prevention and treatment of botulism, caused by botulinum neurotoxin serotype A, from basic research through discovery and preclinical testing. In 2011, with support from an NIAID clinical services contract, XOMA 3AB entered a Phase I human safety trial that was successfully completed in 2013 with no adverse events. In 2013, researchers made significant progress testing XOMA 3B and 3E in nonclinical IND-enabling studies.
- *Pneumonic Plague.* In collaboration with FDA, NIAID is supporting animal studies to determine whether newer antibiotics approved for other uses are also effective against pneumonic plague. Data from NIAID-supported studies played a major role in FDA approval of the first drug for pneumonic plague. In April 2012, an FDA Advisory Committee unanimously recommended FDA approval of ciprofloxacin and levofloxacin as treatments for pneumonic plague. Soon afterward, FDA approved levofloxacin to treat and prevent pneumonic plague, making it the first antibiotic approved under a regulatory approach known as the Animal Rule. This approach may set a precedent for FDA approval of other medical countermeasures under the Animal Rule.
- *Dengue fever.* This mosquito-borne flu-like illness continues to increase in the tropics and subtropics. Phase I trials found that a tetravalent dengue vaccine, developed by NIAID scientists, that is protective against all four dengue viruses is safe and immunogenic.[692] Phase II trials of the vaccine began in Brazil—a dengue-endemic country—in 2013. To support product development, NIAID's vaccine technology has been licensed to several manufacturers in Brazil, India, and Vietnam. NIAID-supported investigators are developing

[691] Durbin AP, et al. *Vaccine*. 2013;31(48):5772–7. PMID: 23968769.

[692] Durbin AP, et al. *J Infect Dis*. 2013;207(6):957–65. PMID: 23329850.

other dengue vaccines using a variety of technologies to improve the delivery methods and the ability to stimulate an immune response to dengue infection. For example, NIAID supported a Phase Ib study to investigate the safety and immunogenicity of the live attenuated dengue vaccine (DENVax) given intradermally by needle or via a needle-free PharmaJet Injector.

Influenza

Another priority in emerging infectious diseases includes seasonal and pandemic influenza. In the U.S., the annual influenza outbreak typically occurs between December and March, and on average, 5–20 percent of the U.S. population contracts influenza every year, with more than 200,000 people hospitalized with complications from influenza infection. Seasonal influenza kills from 3,000 to 49,000 people in the U.S. annually.[693]

Influenza is a significant public health challenge, due in part to the limitations of current influenza vaccines and treatments. For example, resistance to influenza antiviral medications frequently emerges. In recent years, seasonal influenza viruses have become resistant to therapeutic agents, first to adamantanes and then to oseltamivir. Hence, maintaining a pipeline of new and improved anti-influenza medications is critical. In addition, although egg-based manufacturing methods have served well for more than 40 years, they are logistically complex and can lead to delays or shortages if the vaccine strain of influenza virus will not grow efficiently. NIH, BARDA, FDA, CDC, and industry partners have made progress in accelerating the development of additional manufacturing methods, including cell-based manufacturing. These advances will help build a more reliable domestic manufacturing capacity that could be mobilized rapidly in response to the emergence of a pandemic virus.

NIAID conducts and supports a broad range of basic and translational research on influenza, including research and development of new therapies, diagnostics, and vaccines for both seasonal and pandemic influenza strains. Included in these efforts is research to develop a "universal" influenza vaccine that induces a potent immune response to the common elements of the influenza virus that undergo very few changes from season to season and from strain to strain. A universal influenza vaccine has the potential to protect against multiple strains of the virus over several years. In addition, improved antiviral treatments and vaccine manufacturing capacity for influenza could have broad applicability against other infectious diseases.

NIAID also continued to support the Centers for Excellence in Influenza Research and Surveillance (CEIRS) Program,[694] an integrated network of five centers that was established in 2007, building on an NIAID-funded program begun at St. Jude's Children's Hospital in 1999. The CEIRS Program brings together multidisciplinary research teams to expand the NIAID influenza virus surveillance program, both internationally and in the U.S., and to study host immune responses, pathogenesis, the factors that control the emergence and transmission of influenza viruses among animal reservoirs, and the immunological factors that determine whether an influenza virus causes only mild illness or death. The CEIRS Program continually monitors cases of animal and human influenza worldwide to rapidly detect and characterize viruses that may have pandemic potential and to create pandemic vaccine candidates. Ultimately, the CEIRS network will lay the groundwork for new and improved control measures for emerging and reemerging influenza viruses.

The NIAID IRP conducts collaborative influenza research with many public and private sector partners. Major research programs include needle-free pandemic influenza vaccine development through a collaboration with MedImmune, Inc.; basic influenza biology, transmission, and pathogenesis studies in animal models; natural history studies of influenza viruses, including studies of human immune response and pathogenesis; and clinical studies at the NIH CC and elsewhere to characterize and treat severe influenza in various populations using existing and experimental therapeutic strategies.

NIAID ranks the development of a universal influenza vaccine as one of its top scientific priorities because it would eliminate the need to modify the influenza vaccine every season. NIAID intramural researchers recently demonstrated that a "prime-boost" vaccine strategy protected animals

[693] http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm.

[694] http://www.niaid.nih.gov/labsandresources/resources/ceirs/Pages/default.aspx.

from infection with multiple strains of influenza. The vaccine produced an "unnatural immunity," inducing a response to parts of the influenza virus that are conserved between even distantly related virus strains. The recent identification of broadly neutralizing antibodies to influenza virus in humans paves the way toward antibody-mediated cross-protection that might be elicited by vaccination. NIAID's VRC is moving toward the development of a universal flu vaccine while also improving seasonal flu vaccinations with prime-boost regimens. In addition to significant strides in basic research, several preclinical and clinical trials are ongoing. The VRC is actively engaged in developing new vaccine candidates and new vector systems for antigen delivery, viral vector construction and development, structure-based protein immunogen design, and evaluation of vaccine candidates for their effectiveness in inducing potent and broad immune responses in models and in human clinical trials. A universal flu vaccine would be an extraordinary improvement over today's seasonal flu vaccines, resulting in considerable savings and saved lives. In addition, a number of extramural researchers also are working on novel approaches to develop a vaccine that is broadly reactive with multiple influenza subtypes by targeting conserved internal proteins of the virus as well as less variable regions of the hemagglutinin protein.

Antimicrobial Resistance

Many infectious diseases are increasingly difficult to treat as pathogens develop resistance to antimicrobial drugs.[695] For example, in recent years dramatic increases have occurred in antiretroviral drug resistance in HIV, chloroquine and artemisinin resistance in malaria, the emergence of MDR TB and XDR TB, carbapenem-resistant enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

NIH continues to support research into new therapeutic drugs and targets. In 2012, for example, NEI investigators found that certain peptides in the cornea, the transparent tissue at the front of the eye, possess strong antimicrobial qualities that could lead to a new class of low-cost antibiotics. Synthetic versions of the peptides effectively killed bacteria that lead to flesh-eating disease, strep throat, staph infections, diarrhea, and CF lung infections.[696]

Antimicrobial resistance is a significant and increasing health concern, and NIH funds research to understand and address it. Infectious microbes have a remarkable ability to evade and resist the actions of antimicrobial drugs. Combined with the overuse of antibiotics, this has led to an increase in the number of drug-resistant infections. To that end, NIAID supports and conducts research on many aspects of antimicrobial (drug) resistance, from basic research on how microbes develop resistance to clinical trials that translate research from lab findings to potential treatments. Several new research initiatives will advance this important research effort.

Several of these initiatives have been supported through NIAID's Partnerships Program, which has been used to stimulate collaborative efforts and multidisciplinary approaches to advance promising candidate products or platform technologies through the product development pathway. For example, in FY 2012, NIAID supported numerous awards under the Targeting Resistance in Select Gram-Negative Pathogens initiative to stimulate innovation in the discovery and development of novel therapeutic approaches for infections caused by resistant gram-negative bacteria. NIAID also launched the Host-Targeted Interventions as Therapeutics for Infectious Diseases program in FY 2012, which aims to discover and develop therapeutics that target host functions required for infection, replication, spread and/or pathogenesis by priority pathogens. In FY 2012, NIAID issued the Partnerships for Development of Therapeutics and Diagnostics for Biodefense initiative to support preclinical development of lead candidate therapeutics, with a particular interest in therapies targeting antibiotic-resistant pathogens.

With dangerous resistance on the rise, interfering with critical determinants of microbial virulence is considered a promising new approach to control bacterial infection. Phenol-soluble modulins (PSMs) are peptide toxins with multiple key roles in pathogenesis and a major impact on the ability of highly virulent *Staphylococcus aureus* bacteria to cause disease. However, targeting PSMs for therapeutic intervention has been hampered by their multitude and diversity. Work by NIAID intramural researchers revealed a transporter in *S. aureus* that is responsible for the export of all PSM classes, thus representing a single target to interfere simultaneously with the production of all PSMs.[697]

[695] http://www.niaid.nih.gov/topics/antimicrobialresistance/Pages/default.aspx.
[696] Fleiszig SM, et al. *J Clin Invest*. 2012;122(10):3665–77.PMID: 23006328.
[697] Chatterjee SS, et al. *Nat Med*. 2013;19(3):364–7, 2013. PMID: 23396209.

The NIAID-sponsored Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance program[698] explores improved treatment strategies to help reduce the risk of antimicrobial resistance and preserve the effectiveness of existing drugs. NIAID now supports seven large-scale clinical trials through this program to evaluate treatment alternatives for diseases where antibiotics are prescribed most often, including acute otitis media, community-acquired pneumonia, and skin and soft tissue infections caused by community-acquired MRSA.

In June 2013, NIAID launched the Antibacterial Resistance Leadership Group, a major new antimicrobial resistance effort. The Group will develop a research agenda identifying the most important clinical questions in antibacterial resistance, with input from the global antimicrobial resistance research community.

Biodefense and Emerging Infectious Diseases Infrastructure

NIH has invested substantially in the intellectual and physical infrastructure needed to build the nation's capacity for research on biodefense and emerging infectious diseases. This infrastructure is critical to the development of medical countermeasures and has increased the nation's ability to respond to new and re-emerging infectious diseases. This comprehensive infrastructure includes 14 extramural laboratories that provide secure biosafety level (BSL)–4/3/2 and BSL-3/2 biocontainment facilities for research on biodefense and emerging infectious disease agents, respectively. In addition to their own research, the labs support the NIAID Biodefense Research Agenda.

In FYs 2012 and 2013, NIAID continued to support 11 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases. The overall goal of these Centers is to establish and maintain strong infrastructure and multifaceted research and development activities. These activities are providing scientific information and translational research capacity to facilitate the development of the next generation of biodefense countermeasures. To date, more than 3,500 papers have been published by Center-supported scientists. NIAID also funds the Cooperative Centers for Translational Research on Human Immunology and Biodefense, consisting of eight centers that aim to translate research on immunity to infection into clinical applications to protect the public against bioterrorist threats. In addition, the NIAID Vaccine and Treatment Evaluation Units (VTEUs) are clinical sites located at research institutes nationwide that provide extensive clinical trials capacity and expertise. The VTEUs played a key role in testing countermeasures for high-priority infectious diseases.

NIAID offers a broad array of resources for researchers to assist in characterizing and evaluating candidate products. Services are intended to provide critical information to move a product forward, thus lowering the risks of entering the product development pathway:

- The In Vitro Assessment for Antimicrobial Activity program tests antimicrobial activity of products against microbial pathogens and vectors, including those derived from clinical specimens.
- The Animal Models of Infectious Diseases program provides a central resource for three types of services: development and refinement of animal models, in vivo screening, and efficacy testing.
- The Therapeutic Development Services program supports the development of products intended for use in the cure, mitigation, diagnosis, or treatment of disease caused by a pathogen or certain toxins.
- The Vaccine Development Services program supports the development of vaccines; vaccine components, including adjuvants; vaccine delivery systems; other biologics; and BSL-2, BSL-3, and BSL-4 challenge material.

Controlling infectious diseases not only saves lives, but also is essential for building a strong global economy and maintaining international stability. Through its support for research that underpins intervention programs, NIH participates in several efforts, including PEPFAR; the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the Interagency Task Force on Antimicrobial Resistance; and other global initiatives. NIH supports networks of U.S. and international scientists; trains U.S. and foreign investigators to work internationally; and enhances basic biomedical, clinical, and behavioral research capacity and facilities

[698] http://grants.nih.gov/grants/guide/notice-files/NOT-AI-10-020.html.

Figure 3-20. *The NIH Disaster Research Response Project is working to create relevant environmental health data tools and a network of trained research responders. Credit: TFoxFoto/Shutterstock.com.*

around the world. Partnerships, including those with bilateral and multilateral international partners, industry, and host governments, provide extraordinary opportunities for research on vaccines, drugs, and new diagnostics to benefit local populations where the research is done.

NIH funds and partners with institutions and researchers throughout the world and especially in places where diseases such as HIV/AIDS, TB, malaria, dengue, and neglected tropical diseases remain endemic. The following are selected examples of NIAID programs that illustrate the variety of models and platforms made available to support international research.

The International Centers for Excellence in Research (ICER) program was launched in 2002 to develop and sustain research programs in disease endemic countries through partnerships with local scientists. While the ICER program is focused on clinical research in infectious diseases, each center has the capability to address the research and training needs of greatest relevance to the local population. The ICER program builds on experience gained from NIAID's long-standing malaria research collaboration with scientists in Mali, West Africa. Through long-term collaborations with colleagues in Mali, NIAID's Division of Intramural Research has developed a core research program at each site and, over time, has provided opportunities to expand

the research capabilities and programs. The improvement of laboratory and clinical field site infrastructure and the enhancement of information technology capability have been critical components of this effort. NIAID extramural divisions also have provided support to investigators at these sites and aim to continue to support ICER programs through the extramural scientific community. The current ICER sites are located in Mali, Uganda, and India.

South East Asia Infectious Diseases Clinical Research Network was founded in 2005, in response to the global challenge posed by avian influenza, to conduct research on human and avian influenza and other infectious diseases of importance to the region. It has evolved into a collaborative partnership of research institutions in Thailand, Vietnam, and Indonesia; NIAID; Oxford University Center for Tropical Medicine; Wellcome Trust; and WHO. The partnership conducts clinical research addressing emerging threats, increases scientific knowledge, and contributes to improved clinical management of infectious diseases of public health importance. Network partners, including 14 research sites in Thailand, Vietnam, and Indonesia, continue to focus on high-quality, relevant research and development of local research capacity. The intent of the collaboration is to establish and maintain an independent clinical research network of importance to the region, to the U.S., and to the global community.

The Mexican Emerging Infectious Diseases Clinical Research Network is a multisite collaboration between NIAID and the Mexico Ministry of Health that began in September 2009 to conduct clinically relevant and high-quality research on emerging infectious diseases. Among the six sites (five in Mexico City and one in San Luis Potosi), there is capacity to enroll adults and children. Two studies are planned and began enrollment in 2014 and 2015. The long-term strategic plan is to promote the network's sustainability and capacity.

The Indo-U.S. Vaccine Action Program (VAP) was initiated under the Gandhi-Reagan Science and Technology Agreement signed in 1985 and implemented in 1987. The program, co-managed by the Indian Department of Biotechnology and NIAID, supports a broad spectrum of research activities aimed at improving vaccines for diseases of importance to India and of interest to the U.S. Diseases and topics funded under the program include malaria, TB, dengue, immune enhancement, hepatitis C, rabies, the genetics of respiratory syncytial virus, and vaccine development for rotavirus and HIV.

In 2010, NIAID established the International Centers of Excellence for Malaria Research in all malaria endemic regions of the globe in an effort to accelerate the control and elimination of malaria. The program integrates clinical and field approaches with laboratory-based immunologic, molecular, and genomic methods in malaria endemic regions. In 2012, NIAID awarded supplements to support projects focusing on the immune response to malaria, including correlates of protection and the establishment of immune memory.

Public Health Emergency Preparedness

Multiple NIH ICs and grantees conduct research focusing on public health emergency preparedness, response, and recovery issues. These efforts have contributed to a deeper understanding of risks and recovery, providing critical information and countermeasures when public health emergencies strike.

In response to recent disasters and the research conducted in their wake, NIH has committed to fund the *NIH Disaster Research Response Project*.[699] This pilot project, developed by NIEHS in collaboration with NLM, aims to create a disaster research system consisting of environmental health disaster research data collection tools and a network of trained research responders. Elements of the system include epidemiologic questionnaires and clinical protocols, specially trained disaster researchers, environmental health disaster research networks, a roster of subject matter experts, and a support infrastructure that can be activated and deployed during public health emergencies and declared disasters.

Superstorm Sandy was a devastating storm that hit the northeast coast of the United States in fall 2012. Major research institutions in the affected area lost equipment, valuable resources, and significant time in pursuing vital biomedical research. The Office of Extramural Research developed and worked with the NIH ICs to implement a spend plan for $148 million to support five FOAs for restoring the research and research infrastructure to biomedical research institutions affected by Hurricane Sandy. All FOAs were issued in FY 2013, and by September 2013, NIH had issued more than $23 million in awards to assist the restoration of affected biomedical research programs, with the remainder being awarded in FY 2014. In addition, NIEHS's Superfund Worker Training Program (WTP) carried out a process to update state and federal guidance on best practices for the protection of volunteers, homeowners, and cleanup workers during the response to Hurricane Sandy. During 2013, NIEHS WTP released $1.75 million in six supplemental grant funding to provide safety and health training to support recovery, rebuilding, and resilience in Hurricane Sandy–impacted areas. WTP trained more than 1,100 workers in New York and New Jersey as well as provided hurricane health and safety booklets in multiple languages.

In addition, NIH has programs that are focused on medical countermeasures against specific threats, such as biological, chemical, and radiological/nuclear threats. This section focuses on NIH programs on chemical, radiological, and nuclear countermeasures. For information on biological countermeasures, see the section "Infectious Disease and Biodefense" in this chapter.

Chemical Countermeasures

NIH helps coordinate research to develop safe and effective medical countermeasures against chemical weapons. The NIH Countermeasures Against Chemical Threats (CounterACT) research network supports the development of medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disasters. The network is a collaboration between NIH and DoD, including the CounterACT Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. The network supports the development of therapeutics for cyanide, nerve agents, chlorine, sulfur mustard, and radiation exposures.

CounterACT has contributed to several important advances in countermeasures at various stages of preclinical and clinical development, including a major clinical trial demonstration that a fast-acting midazolam auto-injector is highly effective in treating emergency seizures, a promising new cyanide antidote poised for advanced development, and advances in drugs for lung damage from sulfur mustard and for ocular injury from blistering chemicals. CounterACT funding also supported the enhancement of NLM's Chemical Hazards Emergency Medical Management service, an information resource designed for use in mass-casualty incidents involving chemicals, with additional information on chemical countermeasures and supportive agents. Training of personnel remains a critical facet of

[699] http://dr2.nlm.nih.gov/.

effective response to a release of chemical or nuclear/radiological material. For the past 15 years, NIH has worked with the Service Employees International Union to provide high-quality training for hazardous materials emergency responders.

Radiological/Nuclear Countermeasures

NIH continues to lead HHS efforts to sponsor and coordinate research to develop medical countermeasures to mitigate and treat radiation-induced injuries. Many candidate medical countermeasures are in the early stages of discovery, including medical countermeasures for hematopoietic acute radiation syndrome (ARS), GI ARS, radiation-induced lung pneumonitis and fibrosis, and other radiation-induced tissue injuries. Effort to develop radionuclide decorporation agents—specific drugs that remove radioactive isotopes from the body—have matured. Three sponsors for the oral decorporation agents have held successful pre-IND meetings with FDA. Two sponsors with orally bioavailable decorporation agents have submitted IND applications. One additional sponsor was expected to complete an IND submission to treat victims with internal radionuclide contamination from fallout or "dirty bombs" by fall 2015. One sponsor has received FDA approval to proceed with "first-in-man" Phase I clinical safety/pharmacokinetics studies.

NIAID established the Centers for Countermeasures against Radiation program in 2005 in an effort to understand the mechanisms of radiation injuries and develop medical products to diagnose and treat the short- and long-term consequences of radiation exposure after a radiological or nuclear accident or terrorist attack. The program supported more than 300 pilot studies and attracted a number of new investigators from fields outside radiobiology research and developed educational materials in radiation biology for trainees across the U.S. The program has produced more than 500 publications and has filed more than 40 patent applications. The program's efforts helped to revitalize an area of science that had been dormant for many years. To continue these efforts, NIAID will recompete the program for five years of additional funding in FY 2015. It is anticipated that five academic institutions from across the country will be funded.[700]

NIAID also established a product development support services contract to provide medical countermeasure screening and evaluation capabilities in various animal models; develop animal models of hematopoietic and GI ARS as well as delayed effects of acute radiation exposures; and perform IND-enabling studies for promising medical countermeasures, including Good Laboratory Practice and pivotal animal efficacy studies. To continue these efforts, a request for proposal was issued in FY 2014 to recompete the contract for an additional five years.

This contract has been instrumental in developing rodent and nonhuman primate animal models for screening and evaluation of efficacy of candidate medical countermeasures. In 2013, an FDA Advisory Committee reviewed data from an NIAID–funded study on the efficacy of filgrastim in the treatment of the hematopoietic syndrome of ARS that was performed under this contract and voted 17:1 that filgrastim therapy was reasonably likely to produce clinical benefits in humans exposed to radiation following a radiological/nuclear incident. The Committee also recommended that other leukocyte growth factors, including pegfilgrastim, sargramostim, and tbo-filgrastim, could be effective. These actions represent a significant step toward licensure of drug products for a radiation public health emergency indication. NIAID has evaluated a pegylated formulation of filgrastim that could provide dosing advantages over filgrastim in a mass casualty incident and found a 46 percent survival increase in a nonhuman primate model of hematopoietic syndrome of ARS.

NIAID awarded two contracts for further development of candidate medical countermeasures to mitigate or treat GI ARS. The Institute also is reviewing proposals for further development of candidate medical countermeasures to mitigate or treat the thrombocytopenia associated with hematopoietic ARS and will solicit proposals for medical countermeasures for radiation-induced pulmonary injuries.

[700] http://www.niaid.nih.gov/topics/radnuc/Documents/radnucprogressreport.pdf.

NIAID initiated a formal collaboration with the Institut de Radioprotection et de Sûreté Nucléaire in France to develop medical countermeasures for acute and delayed radiation syndromes and triage radiation biodosimetry. The collaboration enables combining expertise in clinical treatment of radiation accident victims and cellular therapies as well as NIAID's advances in animal model development and product testing.

To date, more than 150 candidate medical countermeasures have been identified in the NIAID radiation and nuclear program. Five candidates for hematopoietic ARS, one candidate for GI ARS, one candidate for radiation-induced lung injuries, and one candidate for radionuclide decorporation agent have received HHS and BARDA funding for further advanced product development.

Minority Health and Health Disparities

Scientific and technological discoveries throughout the 20th and 21st centuries have improved the nation's overall health and generated hope for happier, healthier, and longer lives for all. However, some segments of the U.S. population continue to experience elevated morbidity and mortality; disproportionate incidence of disease and disability; and adverse outcomes in cancer, CVD, diabetes, HIV/AIDS, infant mortality, mental illness, and other conditions. These disparities in health are most visible in racial and ethnic minority groups, individuals from socioeconomically disadvantaged backgrounds, and people living in medically underserved areas, including rural communities.

NIH has devoted considerable resources to understanding the root causes of health disparities. As a result of these efforts, a complex web of interconnected and overlapping factors (e.g., biological, behavioral, environmental, societal) have begun to be identified. For example, poverty and lack of education correlate with poor health and lower life expectancy; moreover, discrimination based on racial, ethnic, and linguistic differences in the U.S. not only triggers biological stress, but also creates a barrier to accessing high-quality health care. In addition, some groups are genetically susceptible to certain diseases, and when this inherited biological vulnerability combines with adverse social and environmental factors (e.g., poor diet, pollution, economic stress), these groups exhibit poorer health outcomes. Confronting the interrelated factors that contribute to the existence of health disparities is at the heart of the vigorous efforts NIH is undertaking to make advances in science that will translate into effective prevention and treatment interventions.

Health disparities affecting racial and ethnic minorities and other medically underserved populations are seen across a broad spectrum of diseases and conditions. They represent one of the most persistent public health challenges in the nation. Research findings have shown consistently that many health disparity populations are also less likely than most of the majority population to receive needed health care services, including clinically necessary procedures. Health disparities are frequently associated

Figure 3-21. *A portrait honoring former Representative Louis Stokes is unveiled at the 2012 Summit on the Science of Eliminating Health Disparities. Credit: Ernie Branson, NIH.*

with socioeconomic status (SES) differences and tend to diminish significantly and, in a few cases, disappear when SES factors are controlled. Nevertheless, some racial and ethnic disparities remain even after adjusting for SES differences and other factors related to health care access.

In keeping with its role as the nation's primary steward of biomedical and behavioral research, NIH is firmly committed to eliminating health disparities in the U.S. Since the issuance of the *Report of the Secretary's Task Force on Black and Minority Health* in 1985,[701] NIH has incorporated the goals of improved health for all Americans and the elimination of health disparities in its support of biomedical and behavioral research, research training, research capacity-building, outreach, and research and health information dissemination. Many of these activities are multidisciplinary collaborations involving several NIH ICs or NIH and nonfederal organizations. These efforts not only have advanced health disparities research, but also have facilitated communications among stakeholders and moved the field forward exponentially during the past 25 years.

In December 2012, NIMHD led the *Science of Eliminating Health Disparities Summit*,[702] which hosted hundreds of speakers, unprecedented federal participation from 14 of the 15 executive departments (including all agencies of HHS), and more than 3,000 attendees. The summit attracted almost 2,000 abstract submissions, approximately 100 sessions, and more than 800 scientific posters. In addition to scientific presentations, the summit included open sessions for attendees to provide input on priority areas for the next NIH Health Disparities Strategic Plan.

To address the significant disparities in mental health care related to race and ethnicity, in September 2013, NIMH convened leading experts in disparities research and practice, including representatives from the NIH community, other federal agencies, and researchers charged with improving the nation's mental health equity. At this meeting, "Closing the Gaps: Scaling Up to Reduce Mental Health

[701] U.S. Department of Health and Human Services. Report of the Secretary's Task Force on Black and Minority Health, 1985–1986. Available at: http://resource.nlm.nih.gov/8602912.

[702] http://www.nimhd.nih.gov/summit_site/.

Disparities in the United States,"[703] key discussion topics included the need to address the current workforce shortage in mental health; the need to develop and evaluate mobile and Internet technologies targeting multilingual, underserved populations; and the need to improve access and outcomes for disadvantaged populations with mental disorders.

Throughout its history, NHLBI has been a leader in conducting and supporting research to eliminate health disparities that exist between various segments of the U.S. population. The Institute not only has initiated research projects with significant minority participation to compare health status among various populations, but also has given high priority to programs that focus exclusively on minority health issues. NHLBI epidemiology programs include support for components of NHANES that track prevalence and risk factors of cardiovascular and lung diseases by race and ethnicity; the National Longitudinal Mortality Study, which analyzes socioeconomic, demographic, occupational, and racial differentials in U.S. mortality; and several major studies of heart disease in minority populations. For example, the Jackson Heart Study is the largest prospective, epidemiologic study of CVD among African Americans and serves as a national resource for research on the factors that affect blood pressure, heart disease, stroke, diabetes, and other important diseases that affect African-American health. NHLBI has also been supporting the Strong Heart Study since 1988 to understand CVD mortality and risk factors among Native Americans, with sites in Oklahoma, Arizona, and the Dakotas. Most recently, the Strong Heart Study has been focusing on identifying genetic factors that contribute to risk of cardiovascular and other diseases that affect Native American communities.

Genetic epidemiologic research also includes studies of the genetics of hypertension in populations of West African origin, salt sensitivity in people of Chinese ethnicity, and metabolic traits in Mexican Americans. Understanding racial differences in blood pressure control is an area of major interest for NHLBI, and clinical trials of therapies consistently have included strong representation of minority participants. Understanding the relationships between heart disease and stress induced by environmental, social, or discriminatory influences is another focus of research efforts.

[703] http://www.nimh.nih.gov/research-priorities/scientific-meetings/2013/closing-the-gaps-scaling-up-to-reduce-mental-health-disparities-in-the-united-states.shtml.

Research on aging continues to document the existence of persistent health differentials among older racial and ethnic groups in the U.S., both before and after age 65. NIA remains committed to addressing health disparities and inequities with initiatives supported in partnership with NIMHD as well as with other ICs. One of the Institute's most visible and focused efforts to build the national research infrastructure for reducing and eliminating health disparities is the Resource Centers for Minority Aging Research program,[704] the mission of which includes enhancing professional diversity in minority health research by establishing a research mentoring mechanism in minority health and health disparities, evaluating and developing measurement tools tailored to minority and marginalized population groups, and developing strategies for recruiting and retaining research participants from diverse racial and ethnic backgrounds.[705] Another program, the Healthy Aging in Neighborhoods of Diversity across the Life Span study, is an interdisciplinary, community-based, prospective longitudinal epidemiologic study examining the influences of race and SES on the development of age-related health disparities among socioeconomically diverse Blacks and Whites in Baltimore. This study began in 2004 and is ongoing.[706]

Many diseases and disorders within NIDDK's mission area disproportionately affect minority populations. Therefore, the Institute supports a robust research portfolio to reduce health disparities and improve the health of all people. For example, the Institute's efforts related to type 2 diabetes include the HEALTHY study,[707] which tested a middle school–based intervention for reducing risk factors for type 2 diabetes in youth; the TODAY clinical trial,[708] which is testing different treatment strategies in youth diagnosed with type 2 diabetes; and the Diabetes Prevention Program Outcomes Study,[709] which is following DPP participants to determine the durability of the interventions in preventing or delaying type 2 diabetes and how the interventions affect the development of CVD and other complications of diabetes. Approximately 30–90 percent of participants in these studies are from minority groups that are disproportionately burdened by type 2 diabetes. In addition, NIDDK supports the Type 2 Diabetes Genes Consortium to identify type 2 diabetes risk genes in minority populations.

[704] http://www.rcmar.ucla.edu/.
[705] http://www.rcmar.ucla.edu/index.php.
[706] http://handls.nih.gov.
[707] https://clinicaltrials.gov/ct2/show/NCT00458029.
[708] http://clinicaltrials.gov/show/NCT00081328.
[709] http://clinicaltrials.gov/show/NCT00038727.

Regarding kidney disease, NIDDK-supported researchers have found that blacks with two copies of certain variants in the *APOL1* gene are at increased risk of developing kidney disease, particularly focal segmental glomerulosclerosis and kidney disease related to infection with HIV. These findings explain nearly all of the excess risk of nondiabetic kidney failure in blacks and have important implications for understanding the differences in kidney disease risk across populations. Women from low SES backgrounds, especially from black populations, are particularly susceptible to adverse pregnancy-related outcomes because of a high prevalence rate of obesity. The NIDDK-supported (with co-funding from ORWH) Weight Management in Obese Pregnant Underserved African American Women project is testing a novel lifestyle intervention to help obese socioeconomically disadvantaged black women achieve healthy weight control during and after pregnancy.[710] NIDDK's Weight-control Information Network provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues. It also provides tailored information to high-risk groups, such as through the *Sisters Together: Move More, Eat Better* program guide, which is tailored for black women.[711]

NIMHD supports a variety of research programs to improve minority health and eliminate health disparities at the individual, community, regional, and national levels. For example, the investigator-initiated research project Racial/Ethnic Disparities in Early Life Risk Factors for Childhood Obesity was designed to identify obesity risk factors during pregnancy, infancy, and early childhood and has found that Black and Hispanic 7-year-olds had nearly double the rate of obesity than White 7-year-olds did, as well as early-life risk factors—like rapid infant weight gain, early introduction of solid foods, drinking sugar-sweetened beverages, and lack of exclusive breastfeeding—that appear to explain recognized racial and ethnic disparities among these groups. These findings suggest that designing and implementing interventions to reduce these behavioral risk factors could help eliminate racial and ethnic disparities in childhood obesity.[712]

In another recent study, the NIMHD Center of Excellence at Arizona State University explored substance use among urban American Indian youth by examining the influence of peer, family/parent, school, and neighborhood factors on different types of substance use. The study also examined how these factors varied in students of different genders, grade levels, and heritage. The research uncovered specific risk factors that influenced tobacco, alcohol, and marijuana use—and that these factors differed for different substances. In addition, protective factors, like high neighborhood involvement and positive interactions with teachers, were investigated for each substance.

NIMHD is also focused on supporting the development, implementation, and evaluation of intervention research that uses community-based participatory research methods. NIMHD's Community Based Participatory Research Initiative comprises 40 active intervention phase awards that develop a range of interventions in health disparity communities. In one project, investigators and community collaborators developed and evaluated a church-based HBV screening and vaccination program for Korean Americans. Results indicated significant increases in screening and vaccination rates in participants from intervention churches compared to those attending churches that did not receive the intervention. In another project, the Northwest Portland Area Indian Health Board, in partnership with University of Washington researchers, developed a communitywide intervention to increase use of child safety seats in six Northwest American Indian tribal communities. As a result of the intervention, the use of child safety seats increased by 50 percent in intervention communities, 2.5 times higher than the level of increase in control communities during the same period.

NIMHD supports a variety of collaborative, multisite research initiatives. NIMHD's ongoing Research Centers in Minority Institutions Translational Research Network conducts multisite clinical and translational research on diseases that disproportionately affect minority populations, such as cancer, diabetes, renal disease, infant mortality, HIV/AIDS, and CVDs. In 2013, NIMHD initiated its Transdisciplinary Collaborative Centers for Health Disparities Research (TCC) program to support transdisciplinary coalitions of academic institutions, community organizations, service providers and systems, government agencies, and other stakeholders to conduct minority health and health disparities research at the regional level. In 2012 and 2013,

[710] https://clinicaltrials.gov/show/NCT01768793.
[711] http://win.niddk.nih.gov/.
[712] Taveras, E, et al. *JAMA Pediatr*. 2013;167(8):731–8. PMID: 23733179.

NIMHD funded eight TCCs, including three on the social determinants of health, two on health policy, and three on men's health. One TCC, the Collaborative Research Center for American Indian Health, is bringing together tribal communities and health researchers from a variety of disciplines to develop transdisciplinary research around social determinants of American Indian health, particularly as it applies to public health intervention programming. Another TCC, the Mid-South Transdisciplinary Collaborative Center for Health Disparities Research, is focusing on the pathways to obesity and chronic illness across the life-course for blacks in Alabama, Mississippi, and Louisiana and developing interventions to address these health disparities by examining social, economic, cultural, and environmental factors.

NIMHD has also collaborated with other NIH ICs and agencies to improve minority health and reduce health disparities. The Development and Translation of Medical Technologies that Reduce Health Disparities Initiative, supported by NIMHD and NIBIB, develops and translates medical technologies aimed at reducing disparities in health care access and health outcomes.[713] Technologies targeted by this initiative are remote diagnosis and monitoring; sensors for point-of-care diagnosis; devices for in-home monitoring; portable diagnostic and therapeutic systems; devices that integrate diagnosis and treatment; diagnostics or treatments that do not require special training; devices that can operate in low-resource environments; noninvasive technologies for diagnosis and treatment; and an integrated, automated system to assess or monitor a specific condition. A partnership between EPA and NIMHD through the Environmental Health Disparities Initiative examined the complex relationship between health disparities and the natural, built, social, and policy environments. The initiative has helped develop a public health exposome model to guide research efforts for conceptualizing environmental pathways that affect health disparities and for developing a longitudinal database.[714]

NINDS seeks to reduce the burden of neurological disease for every segment of society. For example, NINDS supports research aimed at better defining stroke risk, incidence, and outcomes in the U.S. and among different subpopulations. Stroke affects certain ethnic and minority populations at a disproportionately higher rate than non-Hispanic Whites: Blacks are at a higher risk of stroke than Whites, and while incidence is decreasing in Whites, the same downward trend is not occurring in Blacks; stroke incidence also is higher in Mexican Americans than in Whites; and in certain areas of the southeastern U.S., stroke mortality is significantly higher than in the rest of the population. Socioeconomic status only accounts for a portion of these disparities, suggesting that biological, cultural, or geographic factors also may play a role. Collection of population-based data helps identify and explain health disparities in stroke and informs the development of preventive interventions that target high-risk populations. For example, in the Reasons for Geographic and Racial Differences in Stroke study, investigators are exploring the geographical and racial influences on stroke risk in a cohort of about 30,000 individuals, of which about half live in the "stroke belt" region of the southeastern U.S. This study has produced nearly 100 publications that have led to better understanding of disparities in stroke in the U.S.[715] NINDS is also supporting research to develop and test culturally tailored interventions that address major contributors to stroke disparities. Four regional programs were funded through an initiative launched in 2012 and include clinical trials of interventions to improve blood pressure control; effectiveness studies testing novel approaches to delivery of care, such as mobile health technologies and transitional care; and observational studies to identify and quantify temporal trends in risk factors. The programs have built partnerships with communities and stakeholders, such as Kaiser Permanente and the AHA's *Get With The Guidelines* program, and include training and education and community outreach, as well as plans for scaling up and disseminating successful interventions.

NINR promotes and improves the health of individuals, families, and communities across the lifespan in a variety of clinical settings and within diverse populations. NINR seeks to advance nursing science by supporting research on the science of health, which focuses on the promotion of health and quality of life. The science of health is based on the premise that individuals would benefit from

[713] https://www.sbir.gov/solicitations/rfa-eb-13-002.

[714] Juarez PD, et al. *Int J Environ Res Public Health*. 2014: 11(12):12866–95. PMID: 25514145.

[715] http://www.regardsstudy.org/.

being actively involved in maintaining their own health through disease prevention and direct participation in illness management. Individuals should be supported in their efforts to understand, interpret, and apply health strategies to promote and manage their own well-being. This approach to health care includes the affirmation that societal and cultural roots are important to health. Thus, the science of health encompasses the investigation of multiple health determinants—including psychological, physiological, genomic, environmental, familial, societal, and cultural factors—and their impact on the health promotion and self-management behavior of individuals within their communities. Some science advances from NINR research related to health equity include: a skill-building program improved parenting skills in ethnically diverse urban families, leading to more positive parenting, improved self-efficacy, and fewer behavioral problems in children; a church-based, culturally targeted self-management program for blacks with type 2 diabetes improved medication adherence, increased healthy eating, and improved blood pressure, blood lipids, physical activity, and waist circumference; and residents from nursing homes in rural areas had higher rates of in-hospital deaths and less hospice use than those in urban areas, highlighting differences in end-of-life care based on geographic location.

NICHD seeks to conduct and support research that improves the health of children, adults, families, communities, and populations. Research supported and conducted by NICHD has helped to explain the unique health needs of different populations and communities, and has brought about novel and effective ways to fulfill these needs and identify factors that can help eliminate health disparities. The NICHD-funded Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) has a current initiative to conduct outreach to minority adolescents at risk for HIV. This initiative builds on an existing infrastructure and knowledge gained from the current ATN, NIH, and CDC collaboration called the Strategic Multisite Initiative for the Identification, Linkage and Engagement in Care of Youth with Undiagnosed HIV Infection (SMILE in CARING for YOUTH) to further improve the identification of minority youth with undiagnosed HIV, enhance links to care activities, and provide better coordination of local services and resources to ensure their retention in care and improve health outcomes.

The prevalence of glaucoma is four times higher in Blacks than in White, and the risk of blindness is up to 10 times higher. An NEI genetics study comparing glaucoma in West African and American populations is pioneering new genetic techniques that require fewer patients for each analysis, thereby shortening the time to bring treatment to those affected. Another study, the African Descent and Glaucoma Evaluation Study, explores racial variations in optic nerve structure and biomechanics among glaucoma patients of African descent, who are at a higher risk for glaucoma than Whites with similar intraocular pressures. In 2013, NEI investigators found that common genetic variants found in Whites were rare in populations of African descent.[716] The study group found that healthy eyes in people of African descent without eye disease performed worse in tests of visual function than did those of European descent, suggesting a need to study how descent might influence visual function and the development of glaucoma.[717] Another NEI initiative to address minority health, the Diabetic Retinopathy Clinical Research Network, conducts trials in community clinics that serve a diverse group of patients with diabetic retinopathy.

Although great progress has been made in improving the oral health of the U.S. population, chronic dental and oral conditions remain among the most common health problems that afflict disadvantaged and underserved communities. NIDCR supports a full spectrum of research studies to identify approaches to improve oral health, taking into account the numerous factors associated with disparities, ranging from the individual to the societal level and from the biological level to health systems and policy levels. For example, at the biological level, one of the factors influencing the high prevalence of aggressive periodontal disease in black children differs in the abundance of certain microbial species. Identification of the specific factors underlying health disparities can best inform the development of early detection, intervention, and treatment strategies.[718] NIDCR-funded researchers are also investigating the role that higher-level factors, such as health literacy, play in oral health. One such study found that literacy varied significantly by race, education level, language use, and a participant's need for help with medical and health materials and forms. People with lower

[716] Liu Y, et al. *Invest Ophthalmol Vis Sci*. 2013;54(9):6248–54.PMID: 23963167.
[717] The ADAGES Group. *Arch Ophthalmol*. 2010;128(5):551–9. PMID: 20457975.
[718] Shaddox LM, et al. *J Dent Res*. 2012;91(10):927–33. PMID: 22863892.

dental and medical health literacy were less likely to receive regular follow-up care than those with higher literacy.[719] Understanding differences in oral health literacy may provide insights into why some ethnic groups have better oral health than others. NIDCR also recognizes the important role of behavior and environment in determining an individual's health status. NIDCR pursues basic and clinical research on determinants of behavior change and also emphasizes training and mentoring opportunities for investigators to acquire the knowledge and skills to conduct rigorous research. For example, NIDCR supports research to investigate the role that dentists can play in communicating to their patients the health risks of certain behaviors, such as eating disorders, alcohol use, and tobacco use.[720, 721, 722]

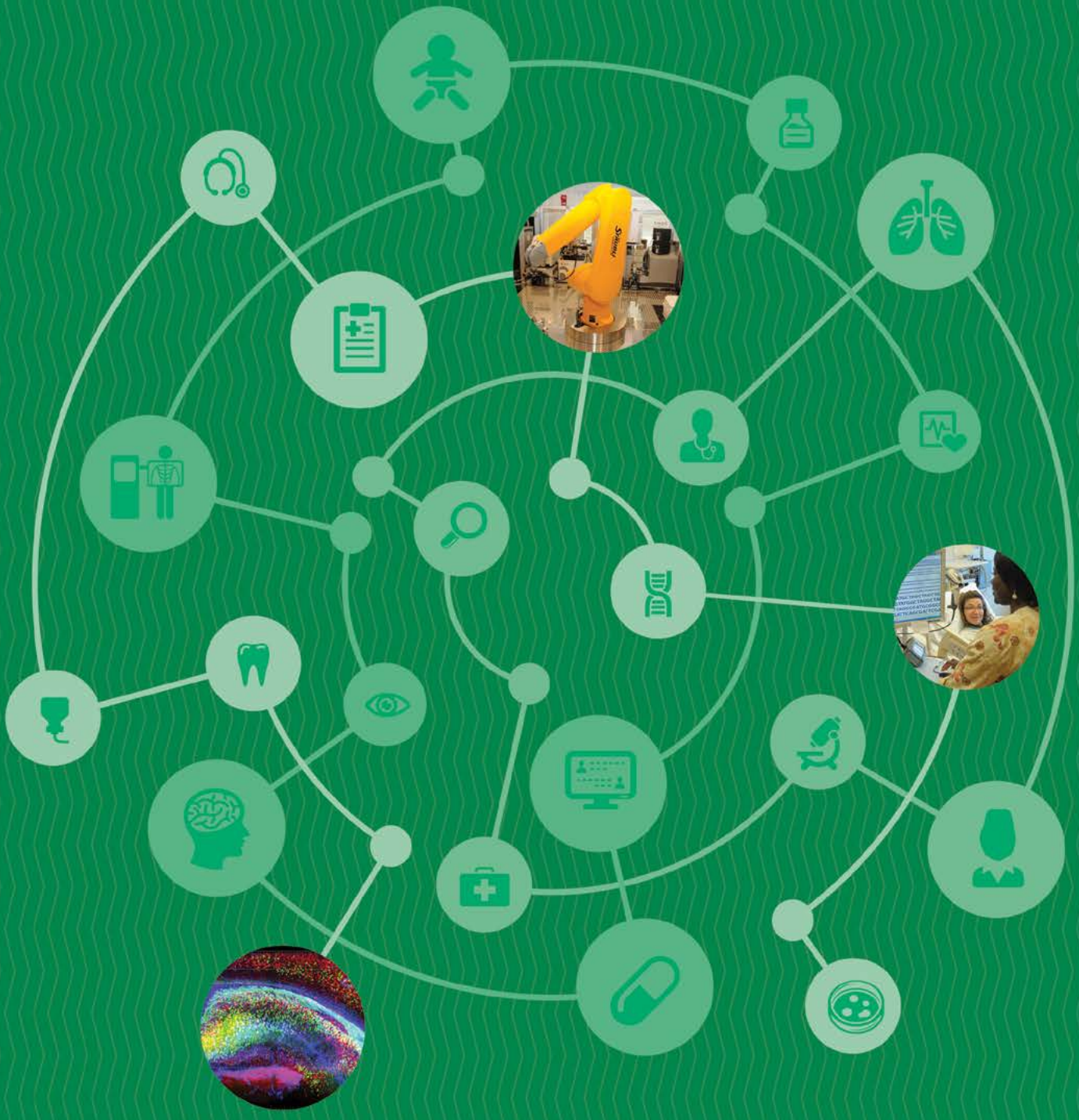
NIEHS invests in a variety of research that investigates the impact of our environment on health disparities in children, Native Americans, women, blacks, Latinos, and rural populations. The Children's Environmental Health Disease and Prevention Research Centers program, supported by NIEHS and EPA, invests in understanding how children are affected disparately by the environment and translates these findings into treatment and intervention strategies. NIEHS researchers have also found an increased incidence of type 2 diabetes in Native American populations exposed to arsenic in drinking water.[723] Appalachian Americans are another underserved population for whom NIEHS-funded researchers are working to decrease health disparities. In one study, genetic surveys were conducted to assess the perceptions of genetic research of three rural Appalachian communities, with the outcome of improving community education materials and how these materials would be best received by these rural populations engaged in genetic research.[724] The NIEHS Partnerships for Environmental Public Health program focuses on research into the risk of increased health burden in populations with inequities in environmental exposure and disease and on translating such research into action to address environmental exposures and health risks of concern to the public. An important component of this program is the promotion of community-based participatory research, by which affected communities are actively involved in the design and conducting of research.

[719] Geltman PL, et al. *Am J Public Health*. 2013;103(8):1516–23. PMID: 23327248.
[720] DeBate RD, et al. *Health Educ Res*. 2013;28(3):472–87. PMID: 23564725.
[721] Neff JA, et al. *J Health Psychol*. 2013;18(4):542–53. PMID: 22837547.
[722] Rindal DB, et al. *Am J Prev Med*. 2013;44(3):260–4. PMID: 23415123.
[723] Kim NH, et al. *Am J Epidemiol*. 2013;177(9):962–9. PMID: 23504692.
[724] Fullenkamp AN, et al. *J Community Genet*. 2013;4(1):9–17. PMID: 22865241.

In addition to serving as the world's largest biomedical library, NLM supports and conducts research, development, and training in biomedical informatics and health information technology. NLM's Environmental Health Information Partnership[725] strengthens institutional capacity to reduce health disparities through use of information technology and environmental health information. The program includes three tribal colleges, the University of Alaska Anchorage, 14 historically black colleges and universities, and three Hispanic-serving institutions. Faculty, staff, and students receive training in NLM's toxicology, environmental health, and other electronic resources; participate in meetings about scientific issues, government and nongovernment programs, and funding opportunities; and engage in local outreach programs to share information in their communities.

NIH's outreach initiatives encompass a wide range of endeavors, including communication and education programs, partnerships, and collaborations with public and private organizations as well as enhancement and expansion of access to information and services among disadvantaged populations. Outreach initiatives span many forms of activity—from creating a new slogan to promote early stroke awareness to developing ways to disseminate science-based oral health information to specific populations, conducting health information outreach initiatives targeting high school students, promoting efforts to disseminate science-based information on obesity and diabetes, and implementing a new, decade-long program devoted to environmental public health. The initiatives also address diverse stakeholder audiences, including students, patients, health care providers, public health educators and officials, policymakers, professional and patient advocacy organizations, and community-based groups. Information and interventions may target specific diseases and conditions, such as HIV/AIDS, obesity, diabetes, digestive diseases, kidney disease, and SIDS, or they may be oriented toward a particular health disparities population subgroup, or both. Information on these initiatives are included on a variety of NIH's health information websites, several of which are available in Spanish.[726, 727, 728, 729, 730, 731]

[725] http://sis.nlm.nih.gov/outreach/enhip.html.
[726] http://www.cancer.gov/espanol.
[727] http://medlineplus.gov/spanish/.
[728] http://aidsinfo.nih.gov/infoSIDA/.
[729] http://ndep.nih.gov/.
[730] http://www.nia.nih.gov/espanol.
[731] http://win.niddk.nih.gov/.



Chapter 4: Centers of Excellence

NIH Centers of Excellence programs are diverse in focus, scope, and origin. In general, they facilitate and coordinate research efforts on a specific disease, a group of diseases, or an area of research. Some were created as NIH-wide initiatives, others by individual ICs and Offices within the (NIH OD), some reflect mergers or redesignations of existing programs, and some were mandated by Congress. The NIH Centers of Excellence programs described in this report are a subset—those established by statutory mandate.

Alzheimer's Disease Centers

Establishment of the Alzheimer's Disease Centers

Based on concerns about the scale of the problems posed by Alzheimer's disease (AD), Congress directed NIH to foster further research related to AD in the Public Health Service Act of 1984. Under section 445 of this act, Congress authorized the establishment of the NIH Alzheimer's Disease Centers (ADCs) program (42 U.S.C. 285e-2). The first ADCs were established through NIH funding in the mid-1980s in response to the congressional directive, information on AD emerging from the work of NIH grantees and other researchers, and the prospect of a medical and social crisis triggered by an explosion of AD cases due to population aging. The principal objectives of the ADC program are to conduct cutting-edge basic, clinical, translational, and social/behavioral research; train the next generation of researchers; and provide information to the public about research findings, access to support services, and opportunities to participate in research. Much of the research takes place through multicenter cooperative studies designed to better understand the causes and effects of AD and to develop and test new interventions for the diagnosis, treatment, and prevention of AD and other age-related neurodegenerative diseases.

How the ADCs Function Within the NIH Framework

NIH currently funds 27 ADCs (Table 4-1). Funding for the ADCs comes from NIA through the P30 (center core grant) and P50 (specialized center grant) mechanisms for five years; Centers compete through a peer review process for additional funding. New applicants for ADC funding compete with existing grantees.

Description of Disease or Condition

AD is the most common form of dementia among older people. It is an age-related, irreversible brain disorder that develops over many years. In the earliest stage, people experience memory loss or other behavioral or cognitive changes, which are usually mild and which are sometimes mistaken for changes that may occur during the normal aging process. As the disease progresses, however, these symptoms gradually lead to dementia, a condition characterized by marked memory loss accompanied by behavior and personality changes. The disease also leads to a decline in other cognitive abilities (such as decision-making and language skills) and eventually to an inability to recognize family and friends and to severe mental decline. These losses are related to the breakdown of the connections between neurons in the brain and the eventual death of many of these cells. For most people who develop AD, symptoms first appear after age 65. AD and other dementing disorders are caused by disease processes that affect the brain, although

age-related brain and body changes can also affect the timing and progression of AD and other dementias.

AD probably has no single cause. The most important known risk factors for the development of AD are age and family history, although education, diet, and environment appear to play a role. Scientists are also finding evidence that some of the risk factors for heart disease and stroke—such as high blood pressure, high cholesterol, and low levels of the vitamin folate—may increase the risk for AD. Increasing evidence also suggests that physical, mental, and social activities may help delay the onset of AD. Although scientists have learned a great deal about AD, they still do not know what causes the disease and have not identified a cure.

Burden of Illness

As many as 5 million Americans, most of them age 65 or older, currently suffer from AD, and experts agree that these numbers will increase significantly if current U.S. demographic trends continue and no effective prevention methods emerge. Economic costs are considerable: An NIA-supported analysis calculated that the cost of caring for people older than age 70 with dementia in the U.S. was between $159 billion and $215 billion in 2010—comparable to, if not greater than, costs of care for heart disease and cancer. Dementia-related costs are expected to rise dramatically in the coming decades with the aging of the baby boom generation.

Our aging society makes AD an especially critical issue, because the number of people with the disease doubles for every five-year age interval beyond age 65. The U.S. Census Bureau estimates that the size of the population age 65 and older will increase to about 72 million people in the next 25 years. Moreover, the fastest-growing segment of the U.S. population consists of people age 85 years or older.

Scope of NIH Activities: Research and Programmatic

NIH's efforts against Alzheimer's disease entered a new era in 2011, with the passage of the National Alzheimer's Project Act (NAPA).[732] This law renewed and strengthened the national effort to find effective treatments for AD and to support people with dementia and their caregivers. As a result, in 2012 the National Plan to Address Alzheimer's Disease outlined objectives and set milestones to achieve these goals. Updated annually, most recently in April 2014, the Plan is a collaborative and constantly reevaluated framework that helps focus efforts to provide better clinical care and to improve services for people with the disease and their families.[733] NIH progress toward achieving the NAPA research milestones is tracked and reported through periodic review of the research funded, results achieved, and new initiatives and programs begun.

The ADC program supports the goals outlined in the NAPA Plan, providing infrastructure and core resources to enhance ongoing research by bringing together basic biomedical, behavioral, social, and clinical scientists to study the causes, progression, prevention, diagnosis, and treatment of AD and to improve health care delivery. ADCs also foster the development of new research approaches and provide training opportunities for research fellows and junior faculty interested in conducting interdisciplinary AD research. By pooling resources and working cooperatively with other ADCs, these centers have produced research findings and developed resources that would have been impossible for investigators working alone.

The ADC program includes two types of centers. NIH requires that all ADCs contain administrative, clinical, data management and statistics, education and information transfer, and neuropathology components, known as "cores," and some centers support other cores by providing specialized resources, such as neuroimaging or genetic data. The 12 Alzheimer's Disease Core Centers provide investigators within and outside the ADC program with access to the broad spectrum of ADC resources, while 15 Alzheimer's Disease Research Centers conduct research projects in addition to providing core resources. Some Centers also support satellite diagnostic and treatment clinics to help recruit patients from underrepresented groups.

Resources shared among ADCs include each center's brain and specimen banks, which consist of well-characterized specimens collected under standardized protocols. ADCs

[732] http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf.

[733] http://aspe.hhs.gov/2014-national-alzheimers-disease-plan-available.

have provided biological samples from patients with AD for hundreds of non-ADC–funded projects.

One of the major resources shared by the ADCs is the National Cell Repository for Alzheimer's Disease (NCRAD), hosted at Indiana University, which collects and stores blood, DNA, and cell lines, as well as well-documented phenotypic data (including age and gender) from families with several members affected by AD and from unaffected control participants. The repository is part of the NIH Alzheimer's Disease Genetics Initiative, which was established to identify genetic risk factors for late-onset AD, and the recently funded Alzheimer's Disease Genetics Consortium (ADGC), which conducts large-scale whole-genome studies on AD. The ADGC itself maintains one of the largest collections of samples available for genome-wide association studies of AD, which are being used to identify the susceptible and protective genes influencing the onset and progression of late-onset disease. These samples are especially valuable because of the rich associated clinical data available for each participant. In 2011, the ADGC was one of four groups that established the International Genetics of Alzheimer's Project, a multinational collaboration to identify and map genes that contribute to the disease.

The ADCs have helped create additional collaborative research resources and projects, including the National Alzheimer's Coordinating Center, the Alzheimer's Disease Cooperative Study, and the Alzheimer's Disease Neuroimaging Initiative. Descriptions of these and other efforts are provided in the following section.

Much of the important progress in AD research in the U.S. during the past 30 years stems from research conducted at or resources provided by the ADCs. ADC scientists have conducted a significant amount of the research on protein processing related to plaque and tangle formation in the brain, hallmarks of Alzheimer's disease. ADC researchers have also identified the common properties of the abnormal proteins associated with several neurodegenerative diseases. In recent years, ADC researchers have evaluated cognitive changes associated with normal aging and the transitions to mild cognitive impairment (early difficulties with thinking and remembering) and dementia. With that research has come a more precise understanding of the timing of various types of cognitive changes, as well as the development of better ways to measure and evaluate those changes. ADC researchers have also identified factors that contribute to changes in cognitive abilities, such as social and physical activity.

Currently, many ADCs are carrying out important studies relating changes in brain structure to the clinical stages of AD. For these studies, researchers are examining patients enrolled in the clinical cores, brain imaging supported by imaging cores, and autopsy evaluations from the neuropathology cores. ADC researchers are also examining relationships and commonalities between AD and cerebrovascular disease or other neurodegenerative diseases, as well as contributions by co-existing non-neurological conditions that occur in people with AD. In addition, the ADCs are exploring commonalities between AD and other dementias, including Parkinson's disease dementia; collaborations are underway with the NINDS-supported Morris K. Udall Centers of Excellence for Parkinson's Disease Research to examine many overlapping scientific and clinical issues.

Another major objective for the ADCs is to recruit racially and ethnically diverse research participants for AD research. To achieve this goal, NIH created the Satellite Diagnostic and Treatment Clinics and linked them to the ADCs. Currently there are 12 active Satellite Clinics recruiting African-American, Hispanic, Native American, and Asian participants. National Alzheimer's Coordinating Center data now show that approximately 20 percent of those enrolled in the ADCs are minorities. Also, the ADCs conduct research on specific concerns related to underserved populations, in cooperation with the NIH-supported Resource Centers for Minority Aging Research.

All ADCs have Outreach, Recruitment, and Education Cores (ORECs) that provide research training for new investigators, as well as outreach to the public, including caregivers. OREC efforts have also been redefined recently to facilitate participant recruitment for large-scale national projects, such as NIA's Alzheimer's Disease Genetics Initiative, Alzheimer's Disease Cooperative Study, Alzheimer's Disease Neuroimaging Initiative, and other clinical trials and initiatives. Collaborations include ongoing interactions with organizations such as the Alzheimer's Association, the HHS Administration on Aging, and NIH's Alzheimer's Disease Education and Referral Center. The ADCs pay

special attention to issues of cultural sensitivity and, where appropriate, structure their information to effectively reach diverse populations, including people for whom English is not a first language.

NIH Funding for FY 2012 and FY 2013

NIH funding for the ADCs was $49.40 million in FY 2012 and $45.94 million in FY 2013.

FY 2012 and FY 2013 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments for the ADCs include the following examples:

National Alzheimer's Coordinating Center (NACC)

In 1999, NIH established the NACC to facilitate collaborative research and standardize procedures among the ADCs. The NACC developed and maintains a large database of standardized clinical and neuropathological research data collected from each ADC. This database is a valuable resource for qualified research scientists for both exploratory and explanatory AD research. The data provided by the NACC support large studies that use patient samples from ethnically, racially, and geographically diverse populations and multiple ADCs. A minimum data set of 67 variables collected from the ADCs contains data on more than 74,000 subjects enrolled since 1984. A much richer longitudinal uniform data set (comprising 725 variables) has been collected from nearly 30,000 participants enrolled since 2005. The NACC itself has funded 30 collaborative multicenter studies and junior investigator awards to use NACC data, and nearly 200 additional research studies funded by other sources have used NACC data in their research.

In 2013, the NACC began accepting voluntary contributions of brain images from ADCs. More than 2,000 images, including those of participants from underrepresented groups, are now included in the database. These images are linked with the Uniform Data Set already collected on all participants and can now be linked to the genotype data from the Alzheimer's Disease Genetics Consortium when that is available and appropriate consent has been obtained. Further information is available on the NACC website.[734]

Today, the NACC database is one of the largest and most comprehensive databases of its type in the world. Data collected by the NACC is freely available for all scientists to use in research studies. In 2013, NACC data became available through the Global Alzheimer's Association Interactive Network, a gateway that allows researchers around the world to obtain access to a vast collection of AD research data, sophisticated analytical tools, and computational resources.

Alzheimer's Disease Cooperative Study (ADCS)

The ADCS is the large clinical trials consortium that is the cornerstone of NIH's major AD clinical trials effort. The consortium expanded from the ADCs and now includes sites throughout the U.S. and Canada. All of the current ADCs are performance sites for the ADCS. The clinical research outcomes of ADCs are inextricable from the outcomes of ADCS. NIH developed the ADCS to advance research on therapeutics that might be useful for treating patients with AD, to improve cognition, slow the rate of decline, delay the appearance of AD, or ameliorate behavioral symptoms. In particular, the ADCS focuses on interventions that industry might not develop, including agents that lack patent protection or are under patent protection but are marketed for other indications, as well as novel compounds developed by individuals, academic institutions, and drug discovery units. More recently, ADCS investigators have begun to explore the use of nonpharmacological interventions. Moreover, the ADCS mission includes the design of new instruments for use in clinical studies and the development of innovative new approaches to clinical study design and AD clinical study analyses.

In 2012, funding for the ADCS was renewed. Building on recent exciting discoveries from the Alzheimer's Disease Neuroimaging Initiative, the ADCS is focusing on new trial approaches that use imaging and other biomarkers in cerebrospinal fluid and plasma to identify participants with AD pathology and to track disease progression

[734] https://www.alz.washington.edu/WEB/mri_main.html.

and treatment response. ADCS investigators are also putting more emphasis on prevention studies, particularly in at-risk but presymptomatic individuals. Additionally, ADCS investigators will be evaluating the effects of a nonpharmacological intervention—exercise—in individuals with mild cognitive impairment in a large multisite trial.

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Most ADCs participate in ADNI, an innovative public–private partnership that is examining the potential of serial MRI, PET, and/or other biomarkers to measure the development and progression of mild cognitive impairment and AD earlier and with greater sensitivity. As is true of the ADCS, the activities and outcomes of ADNI are inextricable from those of the ADCs. ADNI completed its first enrollment phase in August 2007 and is now using MRI and PET imaging and laboratory and cognitive tests to monitor the participants. This stage will generate a comprehensive database that will serve as an important public resource to spur further research. Already, many of the tools and methods developed by the study are fueling similar efforts in Japan, the European Union, and Australia.

In 2009, funding from the American Recovery and Reinvestment Act enabled the ADNI study to move into the "ADNI GO" phase. The ADNI GO research effort is the first study of its kind to focus on participants who exhibit the earliest signs of memory loss in mild cognitive impairment, thought to be a precursor to AD. While the ADNI GO project work continues, the overall ADNI effort has moved into a third phase, known as "ADNI 2," building upon the successes of earlier ADNI phases to identify the earliest signs of Alzheimer's disease.

Research Activities and Outcomes

Since the establishment of the ADC program in 1984, investigators have published thousands of research papers on all aspects of AD and related disorders:[735] A recent analysis identified more than 12,000 scientific papers based on ADC research. Topics have ranged from the disease's biology to its family and societal impact, as well as many studies of diagnosis and treatment. In addition, the ADC program has demonstrated tremendous success in facilitating collaborations across institutions, and collaborative multi-ADC research articles are consistently cited more frequently than AD articles as a whole.

Research accomplishments include the following important studies performed by ADC scientists, highlighting research on biomarkers and AD and carried out by several centers. These are only a few examples from a wide range of research studies conducted by the ADCs.

- *Cerebrospinal Fluid Biomarkers.*[6] NIH-supported researchers, including investigators with ADNI, established a method and standard for testing levels of two candidate biomarkers for AD: tau and beta-amyloid proteins. The researchers have found that levels of these proteins in cerebrospinal fluid (CSF) are correlated with changes in cognition over time and have determined that changes in these two protein levels in CSF may signal the onset of mild AD. This is a significant step toward developing a test to help diagnose the early stages of AD sooner and more accurately and to begin treatment that could delay the development of more severe AD symptoms.
- *New Clinical and Pathological Diagnostic Guidelines.* The identification of strong candidate biomarkers for AD has facilitated the first revision of the clinical diagnostic criteria for AD in 27 years, through a joint effort of NIA and the Alzheimer's Association. The update offers a new paradigm for AD, covering the disease as it gradually progresses over many years, from the earliest preclinical and presymptomatic phase through mild cognitive impairment to advanced dementia. The new guidelines also address the use of imaging and biomarkers to determine whether changes in the brain and body fluids are caused by AD. A separate update addresses diagnosis at autopsy and will help neuropathologists characterize Alzheimer's-related brain changes at death in people who have been diagnosed with dementia and those who have not yet shown clinical symptoms, taking into account that the disease process may begin a decade or two before clinical symptoms such as memory loss appear.
- *New AD Genes.* In the largest genome-wide association study ever conducted in Alzheimer's research, the International Genomic Alzheimer's Project (see above)

[735] Hughes ME, et al. *JAMA Neurol.* 2014;71(4):412-20. PMID: 24514750.

identified 11 new genes associated with increased risk of developing AD. The researchers analyzed previously studied and newly collected DNA data from 74,076 older volunteers with Alzheimer's and those free of the disorder from 15 countries. The new genes (*HLA-DRB5/HLA0DRB1, PTK2B, SLC24A4-0RING3, DSG2, INPP5D, MEF2C, NME8, ZCWPW1, CELF1, FERMT2,* and *CASS4*) join a growing list of gene variants associated with onset and progression of late-onset Alzheimer's. Researchers will continue to explore the roles these genes play.[736]

[736] Lambert JC, et al. *Nat Genet.* 2013;45(12):1452-8. PMID: 24162737.

- *Beta-Amyloid Production and Clearance.* In Alzheimer's disease, a protein fragment called beta-amyloid accumulates in the brain at abnormally high levels. ADC investigators recently found that in the most common, late-onset form of Alzheimer's disease, beta-amyloid is produced in the brain at a normal rate but is not cleared, or removed from the brain, efficiently. In addition to improving the understanding of what pathways are most important in development of Alzheimer's pathology, these findings may one day lead to improved biomarker measures for early diagnosis, as well as a new approach to treating the disease.

Table 4-1. Alzheimer's Disease Centers of Excellence (ADCs)

Institution and Location	Year Established
University of California, San Diego, CA	1984
Massachusetts General Hospital, Boston, MA	1984
Mount Sinai School of Medicine, New York, NY	1984
University of Southern California, Los Angeles, CA	1984
Johns Hopkins University, Baltimore, MD	1984
University of Kentucky, Lexington, KY	1985
University of Pittsburgh, Pittsburgh, PA	1985
University of Washington, Seattle, WA	1985
Washington University, St. Louis, MO	1985
University of Texas Southwestern Medical Center, Dallas, TX	1988
Columbia University Health Sciences, New York, NY	1989
Oregon Health & Science University, Portland, OR	1990
New York University School of Medicine, New York, NY	1990
Mayo Clinic College of Medicine, Rochester, MN	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
University of California, Los Angeles, CA	1991
Boston University Medical Campus, Boston, MA	1996
Northwestern University, Chicago, IL	1996
University of California, Irvine, CA	2000
Arizona Alzheimer's Center, Phoenix, AZ	2001
University of California, San Francisco, CA	2004
Emory University, Atlanta, GA	2005
University of Wisconsin, Madison, WI	2009
University of Kansas Medical Center, Kansas City, KS	2011

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the ADCs

Evaluation Plans

The National Advisory Council on Aging evaluates and makes recommendations for the ADC program every four years. The next evaluation is scheduled for 2017.

Future Directions

NIH plans to have the ADCs continue to emphasize research related to the transition from normal aging to mild cognitive impairment and to full-blown AD, as well as studies of the overlap between AD and other neurodegenerative diseases, instead of concentrating on late-stage AD. In addition, the ADCs will continue to search for biomarkers that predict cognitive decline and diagnose cognitive impairment and dementia.

Claude D. Pepper Older Americans Independence Centers

Establishment of the Claude D. Pepper Older Americans Independence Centers

In 1955, the U.S. Surgeon General established five Geriatric Research and Training Centers to advance research on the health care problems of the elderly and to train future academic leaders in the field of geriatrics. In 1989, Congress passed legislation that redesignated these Geriatric Research and Training Centers as the Claude D. Pepper Older Americans Independence Centers (OAICs), honoring efforts of the former Florida senator and representative to promote the health and well-being of older Americans. Section 445A of the Public Health Service 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 (see Table 4-2).

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 persons. NIH currently supports 14 OAICs (see Table 4-2).

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 the health and independence of older persons. In addition, each OAIC includes a Research Career Development Core to provide research training and career development opportunities in geriatrics and related fields.

Description of Disease or Condition

Age is a primary risk factor for many disabling diseases and conditions. However, human aging is a highly variable process; there is no single disease or condition that is synonymous with aging. Understanding the process of aging is necessary to promote the health and well-being of older adults. Aging research focuses on a range of conditions, including geriatric syndromes (e.g., low muscle mass/strength, mobility disability, and urinary incontinence) and diseases and disorders that are more common among older adults, such as cancer, cardiovascular disorders, stroke, and loss of sensory function.

Burden of Illness

Currently, more than 40 million Americans are more than 65 years old. Of these, nearly 6 million are older than 85, and more than 70,000 have reached their 100th birthday. By 2030, the number of individuals age 65 or older is likely to reach 70.3 million, and this group will comprise 20 percent of the entire U.S. population. The number of the "oldest old," people age 85 or older, is expected to grow to at least 20.9 million by 2050.

Older Americans use more health care than any other age group. As life expectancy increases, the health care system will need to find new ways to address disease and disability during later life.

Scope of NIH Activities: Research and Programmatic

OAICs are designed to develop or strengthen each awardee institution's programs in a key area of aging research, contribute to scientific understanding promoting greater independence for older persons, and offer opportunities for training and career development for young scientists in aging research. The program's ultimate goal is to enhance translation of basic and clinical research on aging into applications and interventions that increase or maintain independence for older persons. 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, or studies to improve understanding of mechanisms contributing to clinical or functional findings).
- Promote translation of clinical research findings into practice in relevant health care settings.
- Collaborate substantially with other OAICs on multicenter projects, such as integrating data systems, supporting multicenter observational studies, and providing infrastructure to support multisite clinical trials, including pragmatic trials.
- Where possible, interface with other NIA-funded programs and centers (e.g., Resource Centers for Minority Aging Research,[737] Centers on the Demography and Economics of Aging,[738] Roybal Centers,[739] Alzheimer's Disease Centers (ADCs),[740] and Nathan Shock Centers[741]).
- Leverage institutional resources, including other NIH-supported programs and centers, to achieve the OAICs' aims efficiently.
- Serve as a source of advice and collaboration to other investigators, both locally and on a large scale, regarding technology, methodology, analysis, or other expertise.

NIH Funding for FY 2012 and FY 2013

NIH funding for the OAICs was $13.28 million in FY 2012 and $12.33 million in FY 2013.

[737] http://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar.
[738] http://www.nia.nih.gov/research/dbsr/centers-demography-and-economics-aging.
[739] http://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging.
[740] http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers.
[741] http://www.nia.nih.gov/research/dab/nathan-shock-centers-excellence.

FY 2012 and FY 2013 Progress Report

Programmatic and Research Activities and Outcomes

- The University of Florida OAIC focuses its aging research on sarcopenia (degenerative age-related muscle loss), including biological mechanisms and contributing factors, as well as the prevention and rehabilitation of disability resulting from sarcopenia. University of Florida researchers examine these issues from interdisciplinary perspectives across the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral and social sciences, and epidemiology.
- The Boston Medical Center at Boston University has established an OAIC in collaboration with Tufts University and the Joslin Diabetes Center. This OAIC fosters collaborations among the universities' multidisciplinary teams of investigators to improve physical mobility by covering the entire spectrum of drug discovery, from target identification to clinical trials and function-promoting therapies.
- The University of Pittsburgh OAIC provides support and resources for investigators to identify interventions to optimize mobility and balance and prevent fall-related injuries in the elderly. This OAIC provides an integrated, multidisciplinary approach by pooling resources from five schools at the University of Pittsburgh. The OAIC is currently conducting several studies of exercise and other interventions to improve balance and mobility, prevent falls, and prevent fall-related injuries.
- Investigators at the Duke University OAIC work to understand and modify different causes of decline in physical functioning. An important focus at the Duke OAIC is to identify biomarkers that may predict risk for functional decline.
- The Johns Hopkins University OAIC supports research to determine the causes of and potential interventions to reduce frailty in older adults. To support frailty intervention studies, the university created a clinical translation unit and a registry of older adults who might be willing to participate in research.
- The theme of the UCLA OAIC is "Preventing Disease and Disability in Vulnerable Populations: A Translational Approach," and the center's investigators address health disparities that vulnerable older persons face because of (1) inadequate understanding of contributors to health and specific illnesses; (2) lack of effective preventive or therapeutic approaches; and (3) inadequate ability to get needed treatment to vulnerable older populations. Through its commitment to translational research, the OAIC also helps overcome the barriers between the promise of basic science research and the delivery of better health.
- The University of Maryland, Baltimore OAIC is studying rehabilitation approaches involving exercise and motor learning. The goal is to improve the recovery of older adults who have suffered a stroke, hip fracture, or other chronic debilitating condition. The OAIC plans to translate these findings into effective community-based rehabilitation programs.
- Research at the University of Texas Medical Branch OAIC focuses on identifying predictors of physical function and recovery from illness in older adults; identifying novel treatments to improve function and accelerate recovery; and using clinical trials to assess the efficacy of these treatments in older patients.
- The Wake Forest University OAIC's mission is to assess the risk factors for physical disability in older adults and to develop and test effective preventive interventions. Several current studies are exploring the effects of diet and exercise on diverse health parameters.
- The Yale University OAIC's research focuses on investigating geriatric health conditions that have several causes. This focus includes single conditions resulting from several contributing factors or affecting several outcomes, as well as multiple conditions occurring at the same time.
- The University of Michigan OAIC, the first OAIC funded by NIH, advances research on health care problems of older adults. Its research emphases include balance, falls, and mobility, as well as pelvic floor impairment in women. In addition, ongoing pilot studies are exploring the genetics of bone chemistry and fragility; a new system for investigating insulin sensitivity; factors modifying the risk of falls in frail and healthy elderly subjects; and the influences of gender and ethnic group on trajectories of alcohol consumption.

- The Mount Sinai School of Medicine OAIC focuses on pain management and palliative care. Ongoing studies are exploring the relationships among postoperative pain, pain treatment, delirium, and cognitive impairment in older adults, as well as the effect of inpatient palliative care consultation teams on hospital costs, hospital and intensive care unit lengths of stay, and readmission rates.
- The OAIC at the University of Arkansas for Medical Sciences studies the causes of declining skeletal and heart muscle function with aging and is developing new interventions for these conditions by targeting protein metabolism and other approaches. The OAIC represents a unique collaborative effort between the University of Arkansas and the University of Oklahoma Health Sciences Center.
- The University of California, San Francisco OAIC focuses on disability in older persons. Its investigators are exploring what leads to disability, how to prevent disability, and how to ameliorate disability's impact on patients and caregivers. This OAIC is particularly interested in the needs of the most vulnerable elders, whether they are vulnerable because of complex medical circumstances or because of adverse social circumstances.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the OAICs

The OAIC Coordinating Center at Wake Forest University facilitates information exchange and research collaborations among OAICs. The Coordinating Center helps develop and implement projects in shared areas of interest. Its major activities include developing and maintaining Web-based resources to facilitate collaboration among OAIC sites and interface with the public; coordinating and enhancing OAIC training programs; and organizing seminars and other activities for senior investigators and trainees at the OAIC Annual Scientific Meeting.

Evaluation Plans

NIH program staff review the progress of each OAIC every year as part of the noncompeting renewal process. In addition, each year, each OAIC must convene an external advisory board of expert scientists from outside the OAIC institution(s) to evaluate the center's progress and suggest any necessary changes in its scientific or administrative directions to achieve its stated goals.

Future Directions

NIH plans to continue to fund new and existing Claude D. Pepper OAICs and to continue to develop and strengthen key areas of aging research in order to discover new and effective ways to promote healthy and productive aging.

Table 4-2. Current Claude D. Pepper Older Americans Independence Centers (OAICs).

Institution and Location	Year Established
University of Michigan, Ann Arbor, MI	1989
University of California, Los Angeles, CA	1991
Wake Forest University, Winston-Salem, NC	1991
Duke University, Durham, NC	1992*
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994
University of Texas Medical Branch, Galveston, TX	1999
Johns Hopkins University, Baltimore, MD	2003
University of Pittsburgh, Pittsburgh, PA	2004
University of Florida, Gainesville, FL	2007
Boston University, Boston, MA	2008
Mount Sinai Medical Center, New York, NY	2010
University of Arkansas for Medical Sciences, Little Rock, AR	2011
University of California, San Francisco, CA	2013

*The Center for the Study of Aging was started at Duke University in 1955; it was redesignated a Claude D. Pepper OAIC in 1992.

Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

Establishment of the Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act, P.L. 107-84) included provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for muscular dystrophy research. In the Omnibus Appropriations for FY 2004 (P.L. 108-199), Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs), in honor of the former Minnesota senator who was a driving force behind the MD-CARE Act. The MD-CARE Act of 2008 officially renamed the centers.

How the Wellstone MDCRCs Function Within the NIH Framework

NIAMS, NINDS, and NICHD fund the Wellstone MDCRCs through the U54 Specialized Centers Cooperative Agreement award mechanism (Table 4-3). NHLBI has also co-sponsored competitions for Wellstone MDCRCs since 2007. It co-funds two centers and plans to support projects within future Wellstone MDCRCs if NIH receives fundable applications that address NHLBI's mission.

A Steering Committee, consisting of NIH science officers and directors and co-directors of each center, coordinates the Wellstone MDCRCs' scientific program. Through annual meetings, the Steering Committee promotes collaborations among center investigators, sharing of resources, and exchange of scientific information.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles. Many dystrophies also affect other organ systems, such as the heart, brain, blood vessels, and gastrointestinal tract (stomach and

intestines). Some forms occur in infancy or childhood, while others typically appear in middle age or later. The Wellstone MDCRCs address, but are not limited to, the following conditions:

- *Duchenne and Becker muscular dystrophies.* Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy and is an X-linked recessive disease. Because it is carried on the X chromosome and its effects are masked by the normal gene, it primarily affects males. Boys who have DMD do not produce the protein dystrophin, which muscle cells need to function properly. DMD usually becomes evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their late teens or 20s. Becker muscular dystrophy (BMD), a less severe disease, occurs when the body produces low levels of dystrophin or forms of dystrophin that do not work properly.
- *Myotonic dystrophy.* Myotonic dystrophy is commonly an adult form of muscular dystrophy, although forms of this disease can affect newborns and other children. It is marked by myotonia (an inability to relax muscles after they contract) and muscle wasting and weakness. Myotonic dystrophy varies in severity and symptoms. It can affect not just skeletal muscles but also other body systems, including the heart, endocrine organs (organs that release hormones, or substances that affect cell function in another part of the body, into the bloodstream), eyes, brain, and gastrointestinal tract.
- *Facioscapulohumeral muscular dystrophy (FSHD).* FSHD initially affects muscles of the face (facio-), shoulders (scapulo-), and upper arms (-humeral). Symptoms usually develop in the teenage years. Some affected individuals become severely disabled. Wasting of muscles of the trunk can lead to life-threatening breathing complications.
- *Congenital muscular dystrophies (CMDs).* The CMDs are a group of muscular dystrophies with different genetic causes. Muscle weakness is present at birth. Several forms are caused by defects in the interactions of muscle cells with the surrounding protein matrix. The brain and other organs are often also affected.
- *Limb-girdle muscular dystrophies (LGMDs).* All LGMDs show a similar distribution of muscle weakness, affecting both upper arms and thighs. Scientists have identified many forms of LGMDs; some affect children, while others affect adults.
- *Miyoshi myopathy.* Miyoshi myopathy causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of LGMD, suggesting that research progress in one form of muscular dystrophy could lead to a better understanding of other forms as well.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs can reduce symptoms and improve quality of life for some individuals. Some drugs, such as corticosteroids, can slow the progression of DMD to some extent but have adverse effects. Several treatments, including gene therapy, cell-based treatments, and strategies to reduce muscle wasting, have shown promise in experiments that used cells and animals. Clinical trials of some therapies have provided encouraging data, including strategies to bypass mutations that cause disease. Clinical trials for drugs to maintain muscle mass, block inflammation, stabilize the muscle membrane, or restore muscle blood vessel function are being planned or are underway.

Burden of Illness

An estimated 1 of every 5,600 to 7,700 males in the U.S. ages 5 through 24 has DMD or BMD.[742] Myotonic dystrophy affects approximately 1 in 8,000 people worldwide,[743] whereas FSHD affects approximately 1 in 20,000 people and affects men and women equally.[744]

The MD-CARE Act called for CDC to collect and analyze information on the number, incidence, correlates, and symptoms of individuals with muscular dystrophy. Results from the project describe the delay between the start of symptoms and definitive diagnosis of DMD.

[742] http://www.cdc.gov/ncbddd/musculardystrophy/data.html.
[743] http://ghr.nlm.nih.gov/condition/myotonic-dystrophy.
[744] www.nlm.nih.gov/medlineplus/ency/article/000707.htm.

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs promote communication and collaboration, develop and share research resources, and help train new muscular dystrophy researchers. Each center can conduct a mixture of basic research to understand the diseases, translational research to turn basic research findings into interventions for patients, and clinical studies to understand how the diseases affect patients and to test interventions. The overall focus of the Wellstone MDCRCs is to integrate activities to develop therapies and other strategies to reduce the burden that muscular dystrophies put on patients and their families.

Collectively, the Wellstone MDCRCs conduct research on various forms of muscular dystrophy, including some not listed above. Examples of research topics addressed by the Wellstone MDCRCs in FY 2012 and FY 2013 follow.

- At the University of Rochester center, researchers are examining cellular and molecular factors that contribute to myotonic dystrophy and are testing potential treatments. When it successfully recompeted for funding in FY 2013, the center expanded its translational research activities to test how a new class of potential drugs affects cardiac function in a mouse model of myotonic dystrophy.
- Research at the University of Iowa center focuses on understanding the causes of and developing treatments for a group of dystrophies called dystroglycanopathies, which are associated with defects in the muscle proteins dystroglycans. The center also provides services through a Muscle Biopsy/Cell Culture/Diagnostics core.
- The center funded through the University of Pennsylvania supports a collaborative group of investigators from the University of Chicago, the University of Florida, and the University of California, Los Angeles. The center's projects focus on the process by which muscle is lost in many of the muscular dystrophies and is replaced with fat and scar-like tissue and on the involvement of inflammation in this process. These studies could lead to novel strategies for the treatment of many different forms of dystrophy.
- In FY 2013, the Wellstone MDCRC at the Boston Biomedical Research Institute moved to the University of Massachusetts, where, in partnership with Children's Hospital in Boston, it continues to study the molecular, genetic, and epigenetic pathologies of FSHD, with the goal of developing potential therapies that can be tested clinically.
- Researchers at the UNC–Chapel Hill center are developing and testing gene therapies for DMD and other muscle disorders. Studies are aimed at designing improved gene therapy vectors with reduced immune response and at testing methods for delivering therapeutic genes to muscle through veins in the legs and arms.
- The Wellstone MDCRC at *Nationwide Children's Hospital* in Columbus, Ohio, is developing strategies to detect immune responses in patients that can occur when DMD-causing mutations are corrected and is determining whether these immune responses may be involved in the success or failure of gene correction therapies.

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 resources from patients with different types of muscular dystrophy, assistance with gene therapy development and production, and tools for measuring muscle health and strength in mouse models.

NIH Funding for FY 2012 and FY 2013

NIH funding for the Wellstone MDCRC program was $9.0 million in FY 2012 and $7.2 million in FY 2013.

FY 2012 and FY 2013 Progress Report

Programmatic Activities and Outcomes

In FY 2013, investigators at the University of Rochester and Boston Biomedical Research Institute Wellstone MDCRCs competed successfully for renewal. The University of Rochester center's interest in how a new class of potential drugs affects cardiac function in a mouse model of myotonic dystrophy qualified the center for co-funding by NHLBI for the next five years. As noted above, Boston

Biomedical Research Institute's Wellstone MDCRC moved to the University of Massachusetts in Worchester, Massachusetts, and Children's Hospital in Boston, where the program will continue through FY 2018.

The UNC Wellstone MDCRC, funded under an earlier Wellstone competition, ended its formal center program in FY 2013. However, many of the center's investigators continue to use support from other grants to explore possible gene therapies for muscular dystrophies and other disorders. Ongoing work by former Wellstone MDCRC researchers includes a NINDS-funded mouse study of an approach to correct the laminin alpha-2–deficient variant of congenital muscular dystrophy, an NHLBI-funded grant to refine gene delivery approaches that could be relevant to a variety of conditions, and a NIAMS-funded grant to improve gene correction therapies by regulating cells of the immune system, which would be applicable to DMD and other forms of dystrophy. Moreover, UNC remains eligible to compete for a future Wellstone MDCRC grant.

The Wellstone MDCRC program has provided opportunities for public–private partnerships in muscular dystrophy. Projects have involved collaborations with, and/or additional support from, companies such as Isis Pharmaceuticals and Genzyme,[745] PTC Therapeutics, and Eli Lilly and Company.[746] The centers also have strong ties with patient advocacy groups and voluntary health organizations that promote and support muscular dystrophy research. Recognizing that input from patients and their families strengthens the Wellstone MDCRC program, NIH required that all Centers competing for FY 2013 funding articulate their plans for community outreach and involvement.

Because training and career development is an important component of the Wellstone MDCRC program, all centers supported in FY 2012 and FY 2013 have formal training and education cores. These facilities provide stipends to predoctoral and postdoctoral researchers and enhance the programs' educational environments.

The Wellstone MDCRC core facilities are national resources for the muscular dystrophy research community. The facilities have been publicized at national meetings and through center websites and the Wellstone MDCRC website.[747] These shared research tools foster collaborations across departments and schools within institutions, and among investigators and health care providers nationwide. Examples of these facilities include:

- The University of Rochester's National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy, which contains information about more than 2,100 patients, provides researchers with cell and tissue samples and clinical information about the donors of these samples. Registry materials have enabled the CDC-based Genetic Testing Reference Material Coordination Program, in collaboration with members of the genetic testing community, and the Coriell Biorepositories, to establish and characterize cell lines that can be used for genetic testing.[748]
- The University of Iowa Wellstone MDCRC oversees a Muscle Tissue/Cell Culture/Diagnostics Core that serves as a national tissue and cell culture resource for research, as well as a laboratory for patient diagnostic and post-intervention biopsy evaluation for clinical trials. A repository contains muscle biopsies from approximately 3,000 patients with a wide variety of neuromuscular disorders. It also contains fibroblast cultures established from more than 100 patients with myopathies, predominantly muscular dystrophies. Diagnostic tests include western blots that can be performed for a limited number of proteins in frozen muscle tissue or in cultured fibroblasts.
- The Physiological Assessment Core at the University of Pennsylvania evaluates muscle integrity and function.[749] The facility's staff conduct measurements that now are the standard for showing whether a new treatment is effective in animals.
- The Nationwide Children's Hospital Wellstone MDCRC provides other members of the Wellstone network with access to well-established assays for standardized quantification of immune responses that can limit the safety and effectiveness of DMD treatments. The core is adapting imaging tools so researchers can monitor these responses in clinical trial participants.

[745] Wheeler TM, et al. *Nature.* 2012;488(7409):111-5. PMID: 22859208.
[746] https://clinicaltrials.gov/ct2/show/NCT01865084.
[747] http://www.wellstonemdcenters.nih.gov/index.htm.
[748] Kalman L, et al. *J Mol Diagn.* 2013;15(4):518-25. PMID: 23680132.
[749] Marshall JL, et al. *Hum Mol Genet.* 2012;21(20):4378-93. PMID: 22798625.

Research Activities and Outcomes

The Wellstone MDCRCs conduct high-quality translational and clinical studies to advance understanding of and therapy development for a variety of muscular dystrophies. Several active clinical trials in the muscular dystrophies were made possible by Wellstone MDCRC findings. Discoveries by investigators affiliated with the Wellstone MDCRC programs also form a basis of new conceptual models, with potential impacts on therapy development for the dystrophies, other neuromuscular diseases, and additional conditions.

Examples of accomplishments in FY 2012 and FY 2013 are provided below:

- The University of Rochester MDCRC has made advances in preclinical therapy development and clinical trial readiness that collectively improve the environment for new therapies for myotonic dystrophy. Investigators have shown preclinical efficacy of antisense oligonucleotides in blocking or eliminating the toxic RNA that forms the basis for myotonic dystrophy. This MDCRC-supported work has fostered a collaboration on antisense oligonucleotide therapeutics with Isis Pharmaceuticals that is now funded by a NINDS translational cooperative agreement. Their natural history studies of the progression of myotonic dystrophy in patients are demonstrating which symptoms are most challenging to patients—findings that can influence the care that today's patients receive and the directions that investigators pursue to develop new therapies in the future.[750]
- Investigators at the University of Florida who are members of the Wellstone MDCRC at the University of Pennsylvania are developing new methods to assess skeletal muscle health in patients with muscular dystrophies, using magnetic resonance imaging and spectroscopy (MRI/S).[751, 752] These investigators are continuing to collaborate with researchers at Oregon Health & Science University and Children's Hospital of Philadelphia in a larger NIH-funded study comparing MRI/S and measures of skeletal muscle function in 100 boys with DMD and 50 healthy controls. Wellstone MDCRC researchers are also conducting preclinical studies of potential treatments for DMD.[753, 754]
- Building on discoveries about the molecular mechanisms responsible for FSHD, researchers at the Boston Biomedical Research Institute MDCRC are learning how complex chromosomal interactions affect disease progression.[755] The researchers are continuing to identify and test candidate biomarkers that could assess how cells, animals, and, ultimately, patients respond to possible therapeutic compounds.[756]
- The University of Iowa MDCRC has led important breakthroughs in the molecular mechanisms of the dystroglycanopathies, a class of muscular dystrophy about which understanding has lagged until the focused efforts of the Iowa group.[757, 758, 759] In 2012, the group discovered a gene that had not previously been associated with Walker-Warburg syndrome, a severe form of congenital muscular dystrophy, and determined that mutations to that gene caused milder disease as well as LGMDs.[760, 761] The Iowa MDCRC is also addressing clinical trial readiness, to ensure that sufficient tools (e.g., biomarkers, trial endpoints) and knowledge (natural history) are in place to run safety and efficacy clinical trials in human subjects.
- Clinical researchers at the UNC–Chapel Hill Wellstone MDCRC have developed a new method for delivery of fluids through veins to skeletal muscles in the legs of dystrophy patients. Previously, the researchers had showed that this is an effective method for delivery of therapeutic genes in a dog model of DMD. As a next step, the scientists have evaluated the safety and feasibility of the delivery method in seven adults who have muscular dystrophy.[762]
- Researchers at the Nationwide Children's Hospital Wellstone MDCRC are preparing to conduct clinical gene transfer studies for DMD and other dystrophies. Investigators are assessing the percent of patients with DMD who are predisposed to develop an immune response against interventions based on gene transfer and whether steroids can ameliorate this reaction.[763]

[750] Heatwole C, et al. *Neurology*. 2012;79(4):348-57. PMID: 22786587.
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[762] Fan Z, et al. *Mol Ther.* 2012;20(2):456-61. PMID: 21772257.
[763] Flanigan KM, et al. *Hum Gene Ther.* 2013;24(9):797-806. PMID: 24010700.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDCRCs

Major review criteria for the Wellstone MDCRCs include the degree to which an institution shows that it can foster substantive collaborations among its researchers and scientists elsewhere that address key issues in muscular dystrophy and the institution's potential to serve as a national infrastructure and training resource. Recognizing the lasting influence that the next generation of muscular dystrophy researchers could have on improving patients' lives, NIH is asking reviewers of the FY 2015 competition to assess the likelihood that candidate Wellstone MDCRCs will prepare trainees for successful, productive scientific careers.

NIH responded to the burgeoning number of basic research findings in muscular dystrophy by requiring that all active Wellstone MDCRCs support research that translates basic findings about the disease to human studies and applications in the clinic. Beginning with the FY 2008 competition, Wellstone MDCRCs are required include at least one clinical research project that involves direct interactions between researchers and muscular dystrophy patients; this requirement will continue for competitive awards issued in FY 2014 and FY 2015.[764, 765]

In addition to therapy development, NIH will encourage studies of the natural history of diseases, biomarker identification and validation, biopsychosocial and health services studies, and other patient-oriented research. Centers may also conduct basic and preclinical translational projects, as long as efforts are directed toward therapy development and other strategies for improving the lives of patients. NIH will continue to monitor the program's coordination and productivity as staff review each center's progress at the time of noncompeting renewal and through regular contact with Wellstone MDCRC leaders through the Steering Committee.

Future Directions

NIH is committed to supporting up to six outstanding Wellstone MDCRCs. In response to a Request for Applications issued in FY 2013,[766] the University of Washington and Fred Hutchinson Cancer Research Center, both based in Seattle, joined the Wellstone MDCRC program in FY 2014. The center supports 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. In FY 2015, NIH plans to hold an open competition and to fund up to three Centers (for a total of up to six active Centers), pending the availability of funds and a sufficient number of highly meritorious applications.[767] Grantees will join the network of Wellstone MDCRCs to translate scientific findings and technological developments into treatments and other health-related improvements for people with muscular dystrophies.

NIH also supports multi-project grants and core centers for muscular dystrophy research at academic institutions that are not Wellstone MDCRCs. NIH is promoting interactions among investigators at the Wellstone MDCRCs and these other institutions to expand the scope and strength of the Wellstone Network.

[764] http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-13-021.html.
[765] http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-15-002.html.
[766] http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-13-021.html.
[767] http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-15-002.html.

Table 4-3. Active Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs), FY 2012–13

Institution and Location	Years active
University of Rochester, Rochester, NY	2003–present
University of Iowa, Iowa City, IA	2005–present
University of Pennsylvania, Philadelphia, PA	2005–present
Boston Biomedical Research Institute, Boston, MA/University of Massachusetts, Worcester, and Children's Hospital, Boston, MA	2008–present
University of North Carolina, Chapel Hill, NC	2008–present
Nationwide Children's Hospital, Columbus, OH	2010–present

National Institute on Minority Health and Health Disparities Centers of Excellence

Establishment of National Institute on Minority Health and Health Disparities Centers of Excellence

The Centers of Excellence (COEs) program supported by the National Institute on Minority Health and Health Disparities (NIMHD) is one of several programs that are central to NIH's scientific investment strategy for addressing and ultimately eliminating health disparities. The Minority Health and Health Disparities Research and Education Act of 2000 (P.L. 106-525) included provisions for the creation of NIMHD to conduct and support research, training, and dissemination of information with respect to racial and ethnic minorities and other populations with health disparities.[768] The statute specifically mandated the creation of COEs in research institutions for the purpose of conducting biomedical and behavioral health disparities research and training.

NIH defines health disparities as differences in the incidence, prevalence, morbidity, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups: African Americans, American Indians and Alaska Natives, Asians, Hispanics, Native Hawaiians and other Pacific Islanders, subpopulations of all of these racial and ethnic groups, socioeconomically disadvantaged populations, and rural populations. NIMHD COEs address health disparities through the following strategies:

- Conducting and supporting basic, clinical, social sciences, health services, and behavioral research.
- Promoting enhancement of research infrastructure and research training.
- Community engagement and dissemination of research information to racial and ethnic minority and other communities that experience health disparities.

[768] Public Law 106-525 designated the National Center on Minority Health and Health Disparities (NCMHD). In FY 2010, NCMHD was re-designated as NIMHD by the Patient Protection and Affordable Care Act (Public Law 111-48).

How the NIMHD Centers of Excellence Function Within the NIH Framework

NIMHD established COEs to create a comprehensive platform in academic institutions to address health disparities in priority diseases and conditions through the fundamental strategies of research, training a diverse scientific workforce, and engaging the community. The COEs program supports the HHS Action Plan to Reduce Racial and Ethnic Health Disparities[769] and the National Prevention Strategy.

Since 2002, NIMHD has supported COEs in 35 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands (Table 4-4 provides the location of current COEs). Initially, the program used three different funding mechanisms: for Resource-Related Centers (R24), Exploratory Centers (P20), and Comprehensive Centers (P60). Using these different funding mechanisms allowed NIMHD to support institutions with varying levels in biomedical research expertise and capacity. This approach also enabled NIMHD to leverage resources to support the capabilities of the geographically and culturally diverse institutions that have longstanding partnerships with local and regional communities and organizations addressing health disparities. The R24 mechanism, which NIMHD no longer uses, enabled institutions with emerging or modest research infrastructures to begin building research capacity to address health disparities. Several institutions that received these R24 awards have since successfully established NIMHD COEs using the P20 mechanism.

NIMHD supported 55 COEs in FY 2012, including 17 ongoing (noncompeting) awards and 38 competing awards, and 53 COEs in FY 2013, all ongoing awards. All COEs funded since 2005 have had project periods of five years. The types of institutions funded directly by the NIMHD COEs program or through partnerships with NIMHD COEs include research-intensive institutions, medical schools, Historically Black Colleges and Universities, Hispanic-serving institutions, tribal colleges/universities, and liberal arts colleges. NIMHD COEs have also been successful in developing novel partnerships with different types of nonacademic

[769] Department of Health and Human Services. HHS action plan to reduce racial and ethnic health disparities [Internet]. Washington (D.C.): HHS; 2011. http://www.minorityhealth.hhs.gov/npa/templates/content.aspx?lvl=lvlid=33&ID=285.

institutions, such as community-based organizations, local departments of public health, and local school districts. These partnerships provide a means for nonacademic institutions to engage in research on improving minority health and/or eliminating health disparities.

Description of Disease or Condition

The research and other COE activities that NIMHD supports are not limited to or focused on a single disease, illness, or condition. The initial NIMHD COEs were focused on health disparities associated with the following priority diseases and conditions: cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity. Subsequent NIMHD solicitations for COEs have broadened the focus to encompass any diseases or conditions that disproportionately affect health disparity populations.

Burden of Illness

The diversity of the contemporary American population is one of the nation's greatest assets. However, the richness of this diversity is challenged by the disproportionate burden of disease and illness that health disparity populations experience. Compelling evidence of the disparities affecting America's racial and ethnic minority, economically disadvantaged, and rural populations includes lower life expectancies and higher rates of cancer, birth defects, developmental disorders, infant mortality, asthma, diabetes, obesity, cardiovascular disease, and stroke. Populations that suffer from health disparities also bear a disproportionate burden of morbidity and mortality associated with HIV/AIDS, autoimmune diseases (such as lupus and scleroderma), poor oral health, sexually transmitted diseases, mental disorders, violence, and substance abuse.

Scope of NIH Activities: Research and Programmatic

Guided by the NIH Health Disparities Strategic Plan and Budget, the scope of activities conducted by NIMHD COEs includes research, development of research capacity (including training and education), and community outreach. This broad scope provides considerable flexibility for COEs to design and implement the multi- and transdisciplinary strategies, studies, interventions, and activities needed to reduce and ultimately eliminate health disparities.

The NIMHD COEs program requires all COEs to establish certain cores:

- An Administrative Core for carrying out and overseeing administrative matters and functions;
- A Research Core for conducting, coordinating, generating, and advancing research on health disparities;
- A Research Training and Education Core for conducting and advancing research training; and
- A Community Engagement Core for engaging communities and others as partners in eliminating health disparities through community participation in research and the joint development and dissemination of effective health information messages and research findings.

NIH Funding for FY 2012 and FY 2013

NIH funding for the NIMHD COE program was $70.8 million in FY 2012 and $62.9 million in FY 2013.

FY 2012 and FY 2013 Progress Report

Programmatic Activities and Outcomes

Significant programmatic accomplishments included establishing 19 new COEs and 19 competing renewals. There were 55 active NIMHD COEs in FY 2012 and 53 in FY 2013 (Table 4-4). NIMHD COEs were also awarded administrative supplements in targeted research areas in FY 2013, including one supplement supported by the NIH Office of Research on Women's Health on sex/gender differences, and one supported by the HHS National Vaccine Program Office.

Research Activities and Outcomes

Funding for the NIMHD COEs has produced several research accomplishments for FY 2012 and FY 2013.

The COE at Case Western Reserve University addresses racial and ethnic disparities in organ donation and kidney transplantation for patients with end-stage renal disease. Research projects within the center are testing a patient navigation model to help patients work through the

transplantation process and a video intervention to increase willingness to serve as an organ donor among individuals from diverse backgrounds. Findings indicate that patients working with a navigator completed three times as many steps in the transplant process as control patients, and the intervention was equally effective among White and African-American patients. In the video intervention, individuals who watched the video were significantly more likely to provide consent for organ donation on their drivers license than individuals who did not view the video, with stronger effects among African-American participants. Future work will address dissemination of these interventions to a broader population.

The COE at the University of Miami is conducting dissemination and implementation research to address racial and ethnic disparities in behaviorally rooted health conditions, including HIV/AIDS, substance abuse, and intimate partner violence and its health consequences. One research project evaluates the effectiveness of an evidence-based intervention, developed and tested by the COE, that is delivered in community public health settings and designed to reduce HIV risk behaviors and sexually transmitted infection (STI) incidence in low-income Hispanic women. A second project evaluates a home-based family intervention to prevent relapse as part of aftercare treatment for Black, Hispanic, and White mothers discharged from residential substance abuse treatment. The COE is also completing a randomized trial of a family-based intervention to prevent substance abuse and HIV/STI risk behaviors among Hispanic youth with psychiatric disorders.

The COE at the University of Hawaii at Manoa addresses health disparities in Native Hawaiian and Other Pacific Islander (NHOPI) populations. One of the COE's research projects examines strategies to reduce preventable hospitalizations related to heart disease and diabetes in NHOPIs. Early findings suggest that disparities in preventable hospitalization are not explained by differences in disease prevalence or insurance coverage. Qualitative data suggest that factors not evidenced from medical records may be driving such disparities, including undocumented substance abuse and mental health disorders, barriers to obtaining prescription medications, and difficulty accessing outpatient clinics during business hours. Other research projects underway examine mechanisms explaining disparities in post-stroke morbidity and mortality after NHOPI patients who have experienced stroke are discharged from the hospital and the impact of financial incentives to improve glycemic control in NHOPI patients with diabetes.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NIMHD COEs

Since their inception in 2002, NIMHD COEs have made progress toward the elimination of health disparities. However, much remains to be done in designing and taking the critical steps needed to translate research findings to meaningful actions that will improve the quality of life experienced by those overburdened by health disparities. Efforts should be targeted toward interventions that work. NIMHD and its COEs cannot and do not act alone; NIMHD has sought and continues to seek new partners and also has encouraged each NIMHD COE to establish partnerships with other NIH-funded centers and programs, other federal agencies, and others committed to eliminating health disparities. In FY 2014 and FY 2015, NIMHD will continue to pursue the ongoing recommendations from previously published Biennial Reports:

- Maximize resources by establishing partnerships with other NIH-funded centers and programs, other federal agencies, and others committed to eliminating health disparities.
- Increase the diversity of the scientific workforce, especially the number of women and biomedical and behavioral scientists from racial and ethnic and other health disparity populations. Focused efforts are particularly important for increasing the number of female scientists and researchers who (1) remain in the sciences beyond the terminal research or professional degree and beyond the postdoctoral or residency stage and who pursue basic or clinical research as a career and (2) serve in leadership and decision-making roles as members of scientific review panels or members of national advisory councils.

- Create opportunities for biomedical and behavioral scientists to work with social scientists, health services researchers, and other public health researchers to more effectively address the transdisciplinary challenges in health disparities elimination and prevention research.
- Enhance the nation's capacity to conduct health disparities research by expanding research and training opportunities.

In addition, now that previous cycles of COEs have conducted foundational work in health disparities, NIMHD will refine future solicitations for COEs to more specifically target the elimination of particular health disparities through translational intervention research and dissemination and implementation research approaches.

Evaluation Plans

NIMHD program staff evaluate the COEs' annual progress by examining each COE's published peer-reviewed articles, books, and book chapters; conferences sponsored and presentations given on health disparities; community engagement activities, such as health fairs and other forums for disseminating health-promotion materials; community participation in research and clinical trials (if applicable); and research training and professional development opportunities provided to emerging scientists. This review determines each COE's progress in meeting the aims and objectives of its grant and helps identify areas of concern that need to be addressed.

Future Directions

The NIMHD COEs program will continue to intensify research efforts to understand, reduce, and eliminate health disparities, with an emphasis on sustaining current partnerships and establishing new ones. The 2012 Summit on the Science of Eliminating Health Disparities involved agencies across the federal government and resulted in several new partnerships for NIMHD and for the NIMHD COEs, as well as significant recommendations for future research themes. With the establishment of new partnerships, NIMHD expects that its COEs will continue to uncover new biomedical and behavioral knowledge for improving minority health and eliminating health disparities across a broad spectrum of diseases and health conditions. It is also expected that NIMHD COEs will embrace future research themes that emphasize the translation of research knowledge into practice and policy.

The COEs will also continue to develop new technologies for measuring the diverse interactions between health disparities and social and policy level factors and new paradigms. The resulting new knowledge and technologies will lead to the development and implementation of bio-psychosocial and other interventions and strategies for improving minority health and eliminating health disparities.

The success of these and future research efforts by the NIMHD COEs will continue to depend, in part, on the development of improved methodological tools, measures, validated instruments, and novel research designs for teasing out the contribution of biologic, behavioral, and social factors, and health policies and practices to health disparities. The success of these COEs will also depend on collaboration with important stakeholders, including community organizations, local government, and health care systems, to ensure that research findings have true community impact. Conducting population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the U.S. will continue to be important. NIMHD will continue to support studies to eliminate or decrease the impact of factors that contribute to the excess risks, morbidity, and mortality associated with living in some regions of the U.S.

Table 4-4. NIMHD Centers of Excellence Active in FY 2012 and FY 2013

Institution and Location
Arizona State University, Tempe, AZ
Case Western Reserve University, Cleveland, OH
Charles R. Drew University of Medicine and Science, Los Angeles, CA
Clark Atlanta University, Atlanta, GA
Columbia University Health Sciences, New York, NY
Dillard University, New Orleans, LA
Florida Agricultural and Mechanical University, Tallahassee, FL
Florida International University, Miami, FL
Georgetown University, Washington, DC
George Washington University, Washington, DC
Georgia Regents University, Augusta, GA
Georgia Southern University, Statesboro, GA
Georgia State University, Atlanta, GA
Howard University, Washington, DC
Jackson State University, Jackson, MS
Johns Hopkins University, Baltimore, MD
Loma Linda University, Loma Linda, CA
Meharry Medical College, Nashville, TN
Morehouse School of Medicine, Atlanta, GA
New York University School of Medicine, New York, NY
North Carolina Central University, Durham, NC
Northern Arizona University, Flagstaff, AZ
Rush University Medical Center, Chicago, IL
State University of New York (SUNY) at Albany, Albany, NY
SUNY Downstate Medical Center, Brooklyn, NY
University of Alabama, Birmingham, AL
University of Arkansas for Medical Sciences, Little Rock, AR
University of California, Los Angeles, CA
University of California, San Diego, CA
University of California, San Francisco, CA
University of Colorado Denver, Aurora, CO
University of Hawaii, Manoa, HI

Institution and Location
University of Illinois, Chicago, IL
University of Kansas Medical Center, Kansas City, KS
University of Maryland, College Park, MD*
University of Massachusetts Medical School, Worcester, MA
University of Miami, Coral Gables, FL
University of Michigan, Ann Arbor, MI
University of Minnesota, Minneapolis, MN
University of New Mexico Health Sciences Center, Albuquerque, NM
University of North Carolina, Greensboro, NC
University of North Texas Health Sciences Center, Fort Worth, TX
University of Oklahoma Health Sciences Center, Oklahoma City, OK
University of Pennsylvania, Philadelphia, PA
University of South Alabama, Mobile, AL
University of South Carolina, Columbia, SC
University of South Dakota, Vermillion, SD
University of South Florida, Tampa, FL
University of Texas Health Sciences Center, Houston, TX
University of Texas, El Paso, TX
University of the Virgin Islands, St. Thomas, VI
University of Washington, Seattle, WA
University of Wisconsin, Madison, WI
Virginia Commonwealth University, Richmond, VA
Wake Forest University Health Sciences, Winston-Salem, NC
Washington State University, Pullman, WA
Weill Medical College of Cornell University, Ithaca, NY
Winston-Salem State University, Winston-Salem, NC

* Originally located at the University of Pittsburgh.

Rare Diseases Clinical Research Network

Establishment of the Rare Diseases Clinical Research Network

The Rare Diseases Clinical Research Network (RDCRN) was established in 2003 by the Office of Rare Diseases Research (ORDR), in collaboration with six NIH ICs. The RDCRN is a collaborative model of rare diseases research that includes patient advocacy groups as research partners. The RDCRN facilitates clinical research in rare diseases through support of (1) collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and trials; (2) training of clinical investigators in rare diseases research; (3) pilot and demonstration clinical research projects; and (4) access to information related to specific rare diseases for basic and clinical researchers, academic and practicing physicians, patients, patient families and friends, and the public. With the December 2011 creation of NCATS, the ORDR and the RDCRN were reestablished under the auspices of that Institute.

ORDR entered a second phase of funding support for the network and a Data Management and Coordinating Center (DMCC); in October 2009, 19 consortia and a DMCC were funded, in collaboration with NINDS, NIAID, NIAMS, NICHD, NIDCR, NHLBI, and NIDDK. Two of the 19 consortia received funds for a two-year period, while the remaining 17 consortia received funds for five years and are listed below at the end of the RDCRN section.

One valued feature of the RDCRN is the Contact Registry, which connects registered patients with rare diseases to the RDCRN so that those patients can be contacted about clinical research opportunities and updates on the progress of the research projects. Patient recruitment through the Contact Registry has helped two research efforts in the Vasculitis Clinical Research Consortium and the Nephrotic Syndrome Study Network complete their recruitment and enrollment efforts. Since August 2009, the public Web pages have received more than 2,786,388 visits, with 1,056,599 visits occurring during 2013 alone.

How the RDCRN Functions Within the NIH Framework

Each consortium develops and carries out clinical protocols for a minimum of three related rare diseases, with guidance from one or more of the participating institutions. A steering committee guides the network. The steering committee consists of the Principal Investigator of each consortium and the DMCC, the RDCRN program coordinator from ORDR, NIH program scientists from the participating NIH ICs, and the chair of the Coalition of Patient Advocacy Groups in the network.

Description of Disease or Condition

A disease is defined as rare if fewer than 200,000 persons in the U.S. have it. There are more than 6,500 rare diseases, and only slightly more than 400 approved drugs and biologic products are available as treatments. Approximately 80 percent of rare diseases are thought to be of genetic origin. It is estimated that at least 50 percent of the patients with rare diseases are children. The National Organization for Rare Disorders estimates that about 1 in 10 people in the U.S. has a rare disease, which translates to as many as 25 million to 30 million people.

The RDCRN website (https://www.rarediseasesnetwork.org) lists all the current and former consortia. Below are the consortia that were funded for the second phase of the RDCRN.

Funded for Five Years

- *Angelman, Rett, and Prader-Willi Syndromes Consortium.* Studies Angelman, Rett, and Prader-Willi syndromes.
- *Autonomic Disorders Consortium.* Studies multiple system atrophy, baroreflex failure, autoimmune autonomic neuropathy, pure autonomic failure, hypovolemic postural tachycardia syndrome, and dopamine beta hydroxylase deficiency.
- *Brain Vascular Malformation Consortium.* Studies familial cerebral cavernous malformations (common Hispanic mutation), Sturge-Weber syndrome (leptomeningeal angiomatosis), and hereditary hemorrhagic telangiectasia (brain arteriovenous malformation).

- *Chronic Graft Versus Host Disease Consortium.* Studies cutaneous sclerosis, bronchiolitis obliterans, late acute graft-versus-host disease, and chronic graft-versus-host disease.
- *Dystonia Coalition.* Studies cervical dystonia, blepharospasm, spasmodic dysphonia, craniofacial dystonia, and limb dystonia.
- *Genetic Disorders of Mucociliary Clearance Consortium.* Studies primary ciliary dyskinesia, cystic fibrosis, and pseudohypoaldosteronism.
- *Inherited Neuropathies Consortium.* Studies Charcot-Marie-Tooth disease (CMT), including CMT1; CMT2, the dominantly inherited axonal neuropathies; and CMT4, the recessively inherited neuropathies.
- *Nephrotic Syndrome Study Network.* Studies focal and segmental glomerulosclerosis, minimal change disease, and membranous nephropathy.
- *North American Mitochondrial Disease Consortium.* Studies aminoglycoside-induced deafness, Alpers syndrome, CoQ deficiency, chronic progressive external ophthalmoplegia, DAD (diabetes and deafness), encephalopathy, encephalomyopathy, familial bilateral striatal necrosis, hepatocerebral disease, Kearns-Sayre syndrome, Leigh syndrome, leukoencephalopathy, Leber's hereditary optic neuropathy, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), myoclonus epilepsy with ragged-red fibers, maternally inherited Leigh syndrome, mitochondrial neurogastrointestinal encephalomyopathy, mitochondrial DNA depletion syndrome, multiple deletions of mitochondrial DNA, NARP (neuropathy, ataxia, and retinitis pigmentosa) syndrome, Pearson syndrome, sensory ataxia neuropathy dysarthria ophthalmoplegia, complex I deficiency, complex II (SDH) deficiency, complex III deficiency, complex IV deficiency, complex V deficiency, and multiple respiratory chain enzyme deficiencies.
- *Porphyrias Consortium.* Studies acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, aminolevulinate dehydratase deficiency porphyria, porphyria cutanea tarda, hepatoerythropoietic porphyria, congenital erythropoietic porphyria, erythropoietic protoporphyria, and X-linked protoporphyria.
- *Primary Immune Deficiency Treatment Consortium.* Studies severe combined immunodeficiency, Wiskott-Aldrich syndrome, and chronic granulomatous disease.
- *Rare Kidney Stone Consortium.* Studies primary hyperoxaluria, APRT deficiency (dihydroxyadeninuria), cystinuria, Dent disease, and Lowe syndrome.
- *Urea Cycle Disorders Consortium.* Studies N-acetylglutamate synthase deficiency, carbamoyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, argininosuccinate synthetase deficiency (citrullinemia I), citrin deficiency (citrullinemia II), argininosuccinate lyase deficiency (argininosuccinic aciduria), arginase deficiency (hyperargininemia), and ornithine translocase deficiency (HHH) syndrome.
- *Vasculitis Clinical Research Consortium.* Studies eosinophilic granulomatosis with polyangiitis (Churg-Strauss), giant cell (temporal) arteritis, granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, polyarteritis nodosa, and Takayasu's arteritis.
- *Lysosomal Disease Network.* Studies aspartylglucosaminuria, late infantile Batten disease, bone disease in the mucopolysaccharidoses (MPS), cystinosis, Danon disease, Fabry disease, Farber disease, fucosidosis, GM1-gangliosidosis types I/II/III, GM2-gangliosidosis, galactosialidosis types I/II, Gaucher disease, glycoproteinoses, Hunter syndrome, Hurler syndrome, I-cell disease, Krabbe disease, late infantile neuronal ceroid, lipofuscinosis, Maroteaux-Lamy syndrome, metachromatic leukodystrophy, Morquio syndrome, mucolipidosis type IV, MPS, mucopolysaccharidosis type IX, multiple sulfatase deficiency, Niemann-Pick disease, Northern epilepsy, Pompe disease, pycnodysostosis, Sandhoff disease, Sanfilippo syndrome (types A , B, C, and D), Scheie syndrome, Schindler disease, sialidosis types I/II, sialuria, Salla disease, Sly syndrome, Tay-Sachs disease, Vogt-Spielmeyer disease, Wolman disease, alpha-mannosidosis types I/II, beta-mannosidosis, and pseudo-Hurler polydystrophy.

- *Sterol and Isoprenoid Research Consortium.* Studies Smith-Lemli-Opitz syndrome, Sjögren-Larsson syndrome, Niemann-Pick disease type C, mevalonate kinase deficiency (mevalonic aciduria, hyperimmunoglobulinemia D with periodic fever syndrome), cerebrotendinous xanthomatosis, and sitosterolemia.
- *Salivary Gland Carcinomas Consortium.* Studies mucoepidermoid carcinoma, adenoid cystic carcinoma, and adenocarcinoma/salivary duct carcinoma.

Funded for Two Years

- *Clinical Investigation of Neurological Channelopathies.* Studies Andersen-Tawil syndrome, episodic ataxias, and non-dystrophic myotonic disorders.
- *Clinical Research Consortium for Spinocerebellar Ataxias.* Studies spinocerebellar ataxia subtypes, including atxia telangiectasia, ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, ataxia with vitamin E deficiency, ataxia of unknown cause, autosomal recessive ataxia of Charlevoix-Saguenay, dentatorubral-pallidoluysian atrophy, Fragile X tremor-ataxia syndrome, Friedreich's ataxia, GAD ataxia, gluten ataxia, mitochondrial ataxia, mitochondrial recessive ataxia syndrome (MIRAS; POLG mutation), multiple system atrophy (cerebellar type), olivopontocerebellar atrophy, paraneoplastic ataxia, spinocerebellar ataxias (types 1, 2, 3 [SCA3/Machado-Joseph disease or MJD], 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 , 25, 26, 27, 28, 29, and 31 and autosomal recessive 4), and sporadic ataxia (onset before 20 years, onset between 20 and 50 years, and onset after 50 years).

Burden of Illness

The burden of illness for all rare diseases is difficult to assess because of the large number of disorders, the complexity of each disease, and the very limited availability of prevalence and incidence data. Overall, the rare diseases listed above and the others being studied are devastating and costly, not only for the patients but also for the families. This is partly because of the diseases' severity and partly because diagnosis can take a long time, often well after symptoms have appeared. Treatment is often unavailable even after a disease is diagnosed. It is impossible to assess the pain, suffering, and lost opportunities experienced by patients and their families. Because of these variables, these rare diseases specifically and others generally represent a disproportionate share of health care spending. In addition, only a limited number of drug companies conduct research into rare diseases, since it is difficult to recover the costs of developing treatments for small, geographically dispersed populations.

Scope of NIH Activities: Research and Programmatic

The RDCRN currently supports natural history studies, clinical trials, and other clinical studies on more than 100 rare diseases at more than 200 clinical centers across the U.S. and internationally, with 25 participating clinical centers located outside of the U.S.

NIH Funding for FY 2012 and FY 2013

NIH funding for the RDCRN was $16.9 million for the 17 consortia and the DMCC in FY 2012 and $17.7 million in FY 2013. The total cost over five years for the RDCRN's second phase is estimated to be $117 million.

FY 2012 and FY 2013 Progress Report

Programmatic and Research Activities and Outcomes

Between 2009 and the end of September 2013, the RDCRN enrolled 18,000 participants in 84 multisite clinical research studies. Consortia funded in the second award cycle enrolled study participants at 175 clinical sites, 25 of which are located outside the U.S., including in the United Kingdom, the Netherlands, Germany, France, Italy, Spain, Switzerland, Canada, Iceland, and Australia. One hundred fifty-one clinical researchers have been trained in rare diseases research. Twenty-four studies have completed subject recruitment and are in their final analysis phase.

One of the RDCRN's successes is an early-stage clinical trial of a heart drug, mexiletine, which was repurposed to treat non-dystrophic myotonia, a rare muscle disorder. With assistance from the RDCRN, researchers at seven

institutions in four countries were able to recruit enough patients with this rare disease for a clinical trial to test the drug.

The network has been exceptionally productive in 2012 and 2013. RDCRN clinical research efforts have resulted in one book, 17 book chapters, three electronic book sections, 114 conference proceedings, 64 conference papers, and 431 journal articles.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the RDCRN

Future Directions

In the fall of 2013, NCATS reissued a FY 2014 funding opportunity announcement for consortia to the RDCRN. NCATS and NINDS also reissued a companion funding announcement for a DMCC. The requirements will build on the experience and lessons learned in the program's earlier years.

Table 4-5. Rare Diseases Clinical Research Network (consortia funded for five years)

Institution and Location	Year Established
University of Pennsylvania, Philadelphia, PA (previously at Boston University School of Medicine, Boston, MA)	2003
Children's National Medical Center, Children's Research Institute, Washington, DC	2003
University of Alabama at Birmingham, AL (previously at Baylor College of Medicine, Houston, TX)	2003
University of South Florida, Tampa, FL	2003
University of North Carolina, Chapel Hill, NC	2004
Columbia University Medical Center, New York, NY	2009
Emory University, Atlanta, GA	2009
Fred Hutchinson Cancer Research Center, Seattle, WA	2009
Mayo Clinic College of Medicine, Rochester, MN	2009
Mount Sinai School of Medicine of NYU, New York, NY	2009
Oregon Health & Sciences University, Portland, OR	2009
University of California, San Francisco, CA (two locations)	2009
University of Michigan, Ann Arbor, MI	2009
University of Minnesota Twin Cities, Minneapolis-St. Paul, MN	2009
University of Texas MD Anderson Cancer Center, Houston, TX	2009
Vanderbilt University Medical Center, Nashville, TN	2009
University of Iowa, Iowa City, IA (previously Wayne State University, Detroit, MI)	2009

Autism Centers of Excellence

Establishment of the Autism Centers of Excellence

CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network estimates that about 1 in 68 children has autism spectrum disorder (ASD).[770] These estimates are based on data collected from health and special education records of children living in 11 areas of the U.S. during 2010. NIH is working to better understand the causes of ASD and to develop treatments for this serious and disabling disorder.

To address this public health challenge, Congress passed the Combating Autism Act of 2006, which emphasized the need to expand research and improve coordination among NIH Centers of Excellence focused on ASD. In response to the Combating Autism Act, the NIH Autism Coordinating Committee (ACC) formed the Autism Centers of Excellence (ACE) program by consolidating the aims of two previous ASD research programs—the Collaborative Programs of Excellence in Autism (CPEA, established in 1997) and Studies to Advance Autism Research and Treatment (STAART, established in 2002 and completed in 2008)—into a single research effort. The ACE program, funding for which began in FY 2007 and FY 2008, focused on identifying the causes of ASD and developing new and improved treatments. The second iteration of the ACE program, launched in FY 2012, focuses on possible causes of ASD, risk and resilience in ASD, children with ASD who have limited speech and communication, preventive interventions and improved treatment, ASD among girls and women, and how genetic and environmental factors are associated with the development of ASD.

[770] Autism and Developmental Disabilities Monitoring Network (CDC). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. MMWR Surveillance Summaries. March 28, 2014 / 63(SS02);1-21. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6302a1.htm.

How the Autism Centers of Excellence Function Within the NIH Framework

The ACE program, which was initiated and funded by scientific programs in NIH, specifically solicited and funded research activities that address priority areas identified by the Strategic Plan for ASD Research developed by the Interagency Autism Coordinating Committee (IACC), a federal advisory committee established under the Children's Health Act and reauthorized under the Combating Autism Act of 2006 and the Combating Autism Reauthorization Act of 2011. The IACC Strategic Plan for ASD Research serves as the roadmap for federal ASD research. Plan priority areas addressed through the ACE program include research on biomarkers, genetic susceptibility, pharmacological treatments, early intervention, and risk and protective factors.

The ACE program comprises several centers and research networks. ACE *centers* foster multidisciplinary collaboration among teams of specialists at a single facility to address a particular research question in depth. Each center conducts interdependent subprojects. ACE *networks* unite researchers at many different facilities throughout the country; working as a unit, each network addresses a particular research question in depth. Because networks encompass multiple sites, they are able to recruit large numbers of participants with ASD, achieving optimal design for treatment trials.

The goals of the ACE program were established by the NIH ACC, a working group composed of the seven NIH ICs (NIMH, NICHD, NIDCD, NIEHS, NINDS, NINR, and NCCAM) that support ASD research and are tasked with enhancing the quality, pace, and coordination of research efforts at NIH in order to find a cure for autism. Five of the ACC ICs (NIMH, NICHD, NIDCD NIEHS, and NINDS) provide funding to the ACE program and share administrative and oversight responsibilities.

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."[771]

[771] Kanner L. *Nerv Child.* 1943;2:217–50.

Over time, growing recognition of a broader range of related disorders led to the use of the term "autism spectrum disorder," which includes several complex neurodevelopmental disorders of early childhood that vary in severity, share common clinical features, and usually persist throughout the lifetime of the individual. Common features include social impairments, verbal and nonverbal communication difficulties, and restricted, repetitive, and/or stereotyped behavior patterns.

A child's primary caregivers are often the first to identify ASD symptoms. As early as infancy, a baby with ASD may be unresponsive to people or focus intently on one item to the exclusion of others for long periods. A child with ASD may appear to develop normally and then withdraw and become indifferent to social engagement. Clinicians can make a reliable ASD diagnosis for most children by age three. 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

ASD causes tremendous economic and social burdens for families and society at large. Although ASD varies greatly in character and severity, it occurs in all ethnic and socioeconomic groups and affects every age group. Currently, no coherent and comprehensive system of care is available for affected individuals. People with ASD may receive private and public services in special education settings, hospitals, university medical centers, and/or residential treatment facilities, among others.

Scientists and economists have estimated that the annual cost of providing care for all Americans with ASD is between $34 billion and $236 billion.[772, 773] The estimated costs over a lifetime for each person total $1.4 million–$3 million.[774, 775] Families often incur large debts for medical and education services that public programs or medical insurance do not cover. In addition, ASD often leads to profound emotional hardships for patients and their families. However, the Affordable Care Act is helping to ease the financial burden that often comes with treating and caring for people with ASD. The law requires that new plans cover autism screening and developmental assessments for children at no cost to parents, and it allows parents to keep their children on their family health insurance until the children turn 26. Insurers are no longer allowed to deny children coverage for pre-existing conditions such as ASD or to set arbitrary lifetime or annual limits on benefits.

Estimates of ASD's prevalence—the number of affected individuals at a given point in time—have increased markedly since the early 1990s. CDC currently estimates that as many as 1 in 68 children has ASD. Boys are approximately five times as likely as girls are to have ASD.[776] However, it is unclear whether incidence—the number of new cases across time in the same population—has also increased. It is also unclear whether the rise in prevalence is due to such factors as the use of different criteria to diagnose ASD, earlier and more accurate ASD diagnoses, or increases in biologic, environmental, or other risk factors. A similar increase in ASD prevalence has occurred in other countries.

Scope of NIH Activities: Research and Programmatic

The centers and networks that make up the ACE program cover a broad range of ASD research areas, including early brain development and functioning, social interactions in infants, rare genetic variants and mutations, associations between autism-related genes and physical traits, possible environmental risk factors and biomarkers, minimally verbal children, underrepresented populations with ASD (such as females and African Americans), and potential new treatments.

In an effort to support and accelerate research in the prevention, cause, diagnosis, and treatment of ASD, NIH created the National Database for Autism Research (NDAR), an informatics system and central data repository. NDAR collects a wide range of data, including phenotypic, clinical, and genomic data, as well as de-identified medical images, from individuals who participate in ASD research, regardless

[772] Ganz ML. *Arch Pediatr Adolesc Med.* 2007;161(4):343-9. PMID: 17404130.
[773] Buescher AV, et al. *JAMA Pediatr.* 2014;168(8):721-8. PMID: 24911948.
[774] Ganz ML. *Arch Pediatr Adolesc Med.* 2007;161(4):343-9. PMID: 17404130.
[775] Buescher AV, et al. *JAMA Pediatr.* 2014;168(8):721-8. PMID: 24911948.
[776] Autism and Developmental Disabilities Monitoring Network (CDC). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. *MMWR* Surveillance Summaries. March 28, 2014;63(SS02);1-21.

of the source of research funding. NDAR provides the infrastructure to store, search across, retrieve, and analyze these varied types of data.

While NDAR receives data from many publicly and privately funded research sources, all ACE centers and networks are expected to contribute their data to NDAR. NDAR also coordinates data access with other federal databases, such as the NIH Pediatric MRI Data Repository and the NIMH Repository and Genomics Resource. The NIMH repository is a national resource for researchers who study the genetics of complex mental disorders, including ASD, and stores human DNA, cell cultures, and clinical data.

NIH Funding for FY 2012 and FY 2013

Five NIH Institutes fund the ACE program: NICHD, NIDCD, NIEHS, NIMH, and NINDS. NIH funding for the ACE program, which includes centers (P50s), a cooperative agreement (U01), and networks (R01s), was $31.65 million in FY 2012 and $26.31 million in FY 2013. The larger amount in FY 2012 reflects funding for the final year of first-round ACE centers and networks.

FY 2012 and FY 2013 Progress Report

Programmatic and Research Activities and Outcomes

The activities and accomplishments of the ACE program (including those centers and networks first funded in FY 2007-2008, and those centers and networks first funded in FY 2012-2013) are highlighted briefly below.

Centers and Networks Funded in the First Round of the ACE Program

- *Yale University.* Researchers are searching for biomarkers of visual engagement and auditory perception in infants at risk for ASD. A recent study from Emory University and the Yale University ACE found that focus on eyes was lower among 2- to 6-month-old infants later diagnosed with ASD, compared to children with typical development. Another investigation found that when viewing significant visual information, such as caregiver faces or peer interaction, typically developing children inhibited eye-blinking earlier than infants who were diagnosed with ASD.[777]
- *University of Illinois at Chicago.* Researchers are studying genetic factors, as well as brain chemicals and brain functions, that could account for repetitive behaviors in people with ASD. The researchers are also testing whether genetic differences influence how individuals respond to certain medications intended to reduce the frequency of these behaviors.
- *University of Washington.* Researchers are investigating genetic and other factors that might increase a person's risk for ASD and factors that might protect people from developing ASD. Researchers at the University of Washington ACE conducted a randomized computerized training program for adults with ASD who showed initial impairment in their ability to recognize faces. The results suggest that adults with ASD who undergo the computerized training can improve their facial recognition and processing skills.[778]
- *University of North Carolina (UNC) at Chapel Hill.* Investigators from the ACE network are studying abnormal processes in early brain development by examining brain images of very young children at risk for developing ASD. A study from this network found evidence of enlarged portions of the amygdala in 6- to 7-year-old children with ASD and that these differences were associated with deficits in social and communicative behavior.[779]
- *University of California, San Diego (UCSD).* Building on earlier breakthrough studies linking brain development to the risk of autism, UCSD ACE investigators recently showed how patches of disorganization in neuronal cells in the prefrontal cortex of children with ASD were traced back to prenatal development. Both the nature of the cellular disorganization and its specific location in the prefrontal cortex provide more precise targets for researchers to examine potential causes and treatments for ASD.[780]

[777] Shultz S, et al. *Proc Natl Acad Sci U S A.* 2011;108(52):21270-5. PMID:22160686.
[778] Faja S, et al. *J Autism Dev Disord.* 2012;42(2):278-93. PMID: 21484517.
[779] Kim JE, et al. *Arch Gen Psychiatry.* 2010;67(11):1187-97. PMID: 21041620.
[780] Stoner R, et al. *N Engl J Med.* 2014;370(13):1209-19. PMID: 24670167.

- *University of California, Los Angeles.* Researchers at this ACE network are studying the causes of and treatments for social communication problems in people with ASD. These researchers will compare two types of intensive daily instruction for children with ASD who use only minimal verbal communication. These researchers plan to enroll 200 children in four cities: Los Angeles, Nashville, New York City, and Rochester, N.Y. Scientists hope this translational research will identify new intervention mechanisms for nonverbal children with autism.
- *University of Pittsburgh.* The University of Pittsburgh ACE is studying how people with ASD learn and understand information.
- *Drexel University.* Researchers with the Drexel University network are studying possible risk factors and biological indicators of ASD before and soon after birth. This project is part of the Early Autism Risk Longitudinal Investigation (EARLI).
- *University of California, Davis.* Recent findings from this ACE showed that starting children with signs of ASD on interventions at an early age and providing more hours of intervention were more critical for improvements in behavior and development than whether the interventions were implemented by parents or in community settings.[781] However, another study demonstrated that a parent-implemented version of the Early Start Denver Model intervention was more effective at reducing parents' stress related to a child's autism diagnosis and improving parents' sense of personal competence than participation in a regular community-provided intervention program.[782]
- *Wayne State University.* Investigators with the Wayne State network sites have completed enrollment for a clinical trial to test the safety and efficacy of buspirone, a drug that targets one type of receptor for serotonin—one of several neurotransmitters that brain cells use to communicate with each other—as an early intervention in children under age 6 who have ASD. A pilot study by the Wayne State researchers showed that buspirone improves social interaction and reduces repetitive behaviors, sensory dysfunction (extreme sensitivity or lack of sensitivity to light, noise, and touch), and anxiety in children with autism.
- *University of California, Los Angeles (UCLA).* Researchers at the UCLA network sites have been utilizing large genomic databases to investigate how rare genetic variations, mutations, and abnormalities affect an individual's risk for autism. Their recent findings show that while common variations in genetic mutation at the individual level contribute less to a person's risk for autism,[783] common inherited variants or mutations at the family level exert stronger effects on ASD risk.[784]

Centers and Networks Funded in the Second Round of the ACE Program

- *University of California, Los Angeles (UCLA).* ACE investigators at the UCLA center will use brain imaging technology to chart brain development among individuals having gene variants suspected of contributing to ASD. The researchers hope to link genetic variants to distinct patterns of brain development, structure, and function in ASD. This ACE center is also examining the development of treatments to improve social behavior and attention in infants and acquisition of language among older children with ASD.
- *Emory University.* The team of researchers at the Emory ACE center will investigate risk and resilience in ASD, with particular interest in factors that lead to positive outcomes or social disability. The team also will conduct randomized clinical trials to develop treatments for 12-month-old children. Other projects will include studies of model systems that will chart brain development of neural networks involved in social interaction and longitudinal studies of how ASD unfolds across early development.
- *Boston University.* Researchers at this ACE center are investigating ASD in children with limited speech. This ACE will use brain imaging technologies in an effort to understand why certain children with ASD do not learn to speak, with the goal of helping these children to overcome this limitation. The research team will also

[781] Rogers SJ, et al. *J Am Acad Child Adolesc Psychiatry.* 2012;51(10):1052-65. PMID: 23021480.
[782] Estes A, et al. *J Autism Dev Disord.* 2014;44(2):353-65. PMID: 23838727.
[783] Anney R, et al. *Hum Mol Genet.* 2012;21(21):4781-92. PMID: 22843504.
[784] Gaugler T, et al. *Nat Genet.* 2014;46(8):881-5. PMID: 25038753.

test new approaches to help young children with ASD acquire language.

- *University of California, Los Angeles.* The first of two UCLA networks will focus its efforts on developing and testing intensive interventions for minimally verbal children with ASD; these interventions are designed to optimize the number of unique socially communicative and unique spoken words. The study will enroll 192 children (ages 5 to 8) across four sites (Los Angeles, Nashville, New York City, and Rochester, N.Y.)
- *University of California, Los Angeles.* The second UCLA ACE network will build on its earlier work identifying genetic variants associated with autism susceptibility, with an important new emphasis on recruiting at least 600 African-American families with a child with ASD. This network will look for gene variants associated with autism in Americans with self-reported African ancestry and will test genetic risk factors identified in White populations to see what role those gene variants may play in autism in people of African descent.
- *Yale University.* An ACE network led by Yale University will investigate the under-examined issue of ASD in women and girls. The project will study a larger sample of girls with autism than has been studied previously and will focus on genes, brain function, and behavior throughout childhood and adolescence. The objectives are to identify causes of ASD and develop new treatments. Additional sites in the network will include UCLA, Harvard, and the University of Washington.
- *UNC–Chapel Hill.* Continuing its efforts as an ACE network, the UNC-based program will conduct longitudinal brain imaging of a combined sample of 600 infants who are at high risk for later developing autism by virtue of having an older sibling with autism. The team's plan to gather more frequent scans throughout infancy and until age 2 will allow investigators to gain a greater understanding of early brain development in children with ASD.
- *UNC–Chapel Hill.* The second ACE network from UNC will test whether treatments with oxytocin nasal spray can improve social interaction and communication in children with ASD. Oxytocin is a neuropeptide used by brain cells to communicate and has been associated with social behaviors. The researchers plan to enroll 300 children (ages 3 to 17) with ASD from Boston; Chapel Hill and Durham, N.C.; Nashville; New York City; and Seattle.
- *Mount Sinai School of Medicine.* These ACE network investigators will conduct a critical study to understand how genetic and environmental factors influence the development of autism. The team of American and international researchers will analyze detailed records and biospecimens from 4.5 million births involving 20,000 cases of ASD from 7 countries (the U.S., Australia, Denmark, Finland, Israel, Norway, and Sweden). The analysis will span three generations and involve grandparents, parents, aunts, uncles, siblings, and cousins.
- *Harvard Medical School.* This network will recruit patients with tuberous sclerosis complex (TSC), a rare genetic disease that causes tumors in the brain and other vital organs.[785] Patients with TSC have an increased risk for developing autism. The researchers will track brain development in infants diagnosed with TSC to gain insights into how autism develops.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NIH COEs

Evaluation Plans

The Combating Autism Act of 2006 and the NIH Reform Act of 2006 require that NIH conduct periodic reviews of the ACE program. To implement this requirement, NIH formed the Autism Evaluation Implementation Oversight (AEIO) working group, with membership comprising Planning and Evaluation Officers at the five NIH Institutes that provide financial support and scientific expertise to the ACE program (NIMH, NICHD, NINDS, NIEHS, and NIDCD). In 2008 and 2009, the group conducted a feasibility study to evaluate the ACE program, and they prepared a report in 2010. The objectives of the study were to (1) determine the availability of data and the feasibility of answering key questions about the ACE program and (2) obtain baseline data on the ACE program. Based on the results of the feasibility study, the AEIO has outlined plans to periodically update the baseline data.

[785] http://www.ninds.nih.gov/disorders/tuberous_sclerosis/tuberous_sclerosis.htm.

In 2013, the AEIO began a process evaluation of the ACE program, to assess the implementation and outputs of the program during its intermediate phase, from 2010 through mid-2014. This evaluation will capture new information about the program since the feasibility study was conducted, including outputs of both prior and current ACEs and implementation of the program as currently funded. Specifically, the process evaluation will review research, training, and dissemination activities of the ACE centers and networks, as well as research collaborations and community partnerships. This evaluation will help determine whether the ACE program is positioned to achieve the program goals and have an impact on the field of ASD research.

Future Directions

In 2013, as in the prior three years, the NIH ACC convened a two-day meeting at which investigators presented progress toward the goals of their ACEs and exchanged ideas for collaborations. Some sessions addressed data-sharing options through NDAR, with time allotted for a question-and-answer period with NDAR staff. ACE principal investigators and project principal investigators, as well as core directors and data managers, attended the meeting. Principal investigators were encouraged to invite K award (career development grant) recipients, fellows, and postdoctoral students from their laboratories.

Table 4-6. Autism Centers of Excellence (ACEs).

Institution and Location	Year Started	
	First Round	Second Round
University of California, Davis, CA	2007	2013
University of California, Los Angeles, CA (1)	2007	2012
University of California, Los Angeles, CA (2)	2008	2013
University of California, Los Angeles, CA (3)	—	2012
University of California, San Diego, CA	2007	—
University of Illinois at Chicago., Chicago, IL	2007	—
University of North Carolina, Chapel Hill, NC (1)	2007	2012
University of North Carolina, Chapel Hill, NC (2)	—	2012
University of Pittsburgh, Pittsburgh, PA	2007	—
University of Washington, Seattle, WA	2007	—
Yale University, New Haven, CT	2008	2012
Wayne State University, Detroit, MI	2008	—
Drexel University, Philadelphia, PA	2008	—
Boston University, Boston, MA	—	2012
Emory University, Atlanta, GA	—	2012
Harvard Medical School, Cincinnati Children's Hospital, and University of Cincinnati, Boston, MA and Cincinnati, OH	—	2012
Mount Sinai School of Medicine, New York City, NY	—	2012

Appendix A: Legal Mandate for the Biennial Report

PUBLIC HEALTH SERVICE ACT

APPOINTMENT AND AUTHORITY OF DIRECTOR OF NIH (relevant excerpt)

SEC. 402(b)

In carrying out the purposes of section 301, the Secretary, acting through the Director of NIH—

(7)(A) shall, through the Division of Program Coordination, Planning, and Strategic Initiatives—

(ii) include information on such research in reports under section 403; and

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BIENNIAL REPORTS OF DIRECTOR OF NIH

SEC. 403

(a) IN GENERAL.—The Director of NIH shall submit to the Congress on a biennial basis a report in accordance with this section. The first report shall be submitted not later than 1 year after the date of the enactment of the National Institutes of Health Reform Act of 2006. Each such report shall include the following information:

(1) An assessment of the state of biomedical and behavioral research.

(2) A description of the activities conducted or supported by the agencies of the National Institutes of Health and policies respecting the programs of such agencies.

(3) Classification and justification for the priorities established by the agencies, including a strategic plan and recommendations for future research initiatives to be carried out under section 402(b)(7) through the Division of Program Coordination, Planning, and Strategic Initiatives.

(4) A catalog of all the research activities of the agencies, prepared in accordance with the following:

(A) The catalog shall, for each such activity—

(i) identify the agency or agencies involved;

(ii) state whether the activity was carried out directly by the agencies or was supported by the agencies and describe to what extent the agency was involved;

and

(iii) identify whether the activity was carried out through a center of excellence.

(B) In the case of clinical research, the catalog shall, as appropriate, identify study populations by demographic variables and other variables that contribute to research on minority health and health disparities.

(C) Research activities listed in the catalog shall include, where applicable, the following:

(i) Epidemiological studies and longitudinal studies.

(ii) Disease registries, information clearinghouses, and other data systems.

(iii) Public education and information campaigns.

(iv) Training activities, including—

(I) National Research Service Awards and Clinical Transformation Science Awards;

(II) graduate medical education programs, including information on the number and type of graduate degrees awarded during the period in which the programs received funding under this title;

(III) investigator-initiated awards for postdoctoral training and postdoctoral training funded through research grants;

(IV) a breakdown by demographic variables and other appropriate categories; and

(V) an evaluation and comparison of outcomes and effectiveness of various training programs.

(v) Clinical trials, including a breakdown of participation by study populations and demographic variables and such other information as may be necessary to demonstrate compliance with section 492B (regarding inclusion of women and minorities in clinical research).

(vi) Translational research activities with other agencies of the Public Health Service.

(5) A summary of the research activities throughout the agencies, which summary shall be organized by the following categories, where applicable:

(A) Cancer.

(B) Neurosciences.

(C) Life stages, human development, and rehabilitation.

(D) Organ systems.

(E) Autoimmune diseases.

(F) Genomics.

(G) Molecular biology and basic science.

(H) Technology development.

(I) Chronic diseases, including pain and palliative care.

(J) Infectious diseases and bioterrorism.

(K) Minority health and health disparities.

(L) Such additional categories as the Director determines to be appropriate.

(6) A review of each entity receiving funding under this title in its capacity as a center of excellence (in this paragraph referred to as a "center of excellence"), including the following:

(A) An evaluation of the performance and research outcomes of each center of excellence.

(B) Recommendations for promoting coordination of information among the centers of excellence.

(C) Recommendations for improving the effectiveness, efficiency, and outcomes of the centers of excellence.

(D) If no additional centers of excellence have been funded under this title since the previous report under this section, an explanation of the reasons for not funding any additional centers.

(b) REQUIREMENT REGARDING DISEASE-SPECIFIC RESEARCH ACTIVITIES.—
In a report under subsection (a), the Director of NIH, when reporting on research activities relating to a specific disease, disorder, or other adverse health condition, shall—

(1) present information in a standardized format;

(2) identify the actual dollar amounts obligated for such activities; and

(3) include a plan for research on the specific disease, disorder, or other adverse health condition, including a statement of objectives regarding the research, the means for achieving the objectives, a date by which the objectives are expected to be achieved, and justifications for revisions to the plan.

(c) ADDITIONAL REPORTS.—In addition to reports required by subsections (a) and (b), the Director of NIH or the head of a national research institute or national center may submit to the Congress such additional reports as the Director or the head of such institute or center determines to be appropriate.

SCIENTIFIC FRAMEWORK FOR RECALCITRANT CANCERS (relevant excerpt)

SEC. 417G

(d) REPORTING.—

(1) BIENNIAL REPORTS.—The Director of NIH shall ensure each biennial report under section 403 includes information on actions undertaken to carry out each scientific framework developed under subsection (a) with respect to a recalcitrant cancer, including the following:

(A) Information on research grants awarded by the National Institutes of Health for research relating to such cancer.

(B) An assessment of the progress made in improving outcomes (including relative survival rates) for individuals diagnosed with such cancer.

(C) An update on activities pertaining to such cancer under the authority of section 413(b)(7).

OFFICE OF RESEARCH ON WOMEN'S HEALTH (relevant excerpts)

SEC. 486(d)(5) ADVISORY COMMITTEE.—

(A) The Advisory Committee shall prepare a biennial report describing the activities of the Committee, including findings made by the Committee regarding—

(i) compliance with section 492B;

(ii) the extent of expenditures made for research on women's health by the agencies of the National Institutes of Health; and

(iii) the level of funding needed for such research.

(B) The report required in subparagraph (A) shall be submitted to the Director of NIH for inclusion in the report required in section 403.

SEC. 486B BIENNIAL REPORT

(a) IN GENERAL.—With respect to research on women's health, the Director of the Office shall, not later than February 1, 1994, and biennially thereafter, prepare a report—

(1) describing and evaluating the progress made during the preceding 2 fiscal years in research and treatment conducted or supported by the National Institutes of Health;

(2) describing and analyzing the professional status of women physicians and scientists of such Institutes, including the identification of problems and barriers regarding advancements;

(3) summarizing and analyzing expenditures made by the agencies of such Institutes (and by such Office) during the preceding 2 fiscal years; and

(4) making such recommendations for legislative and administrative initiatives as the Director of the Office determines to be appropriate.

(b) INCLUSION IN BIENNIAL 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.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH (relevant excerpt)

SEC. 492B

(f) REPORTS BY ADVISORY COUNCILS.—The advisory council of each national research institute shall prepare biennial reports describing the manner in which the institute has complied with this section. Each such report shall be submitted to the Director of the institute involved for inclusion in the biennial report under section 403.

HUNTER KELLY NEWBORN SCREENING RESEARCH PROGRAM (relevant excerpt)

SEC. 1116

(c) REPORTS.—The Director is encouraged to include information about the activities carried out under this section in the biennial report required under section 403. If such information is included, the Director shall make such information available to be included on the Internet Clearinghouse established under section 1112.

MICROBICIDE RESEARCH (relevant excerpt)

SEC. 2351A

(a) FEDERAL STRATEGIC PLAN.—The Director of the Office shall—

(1) expedite the implementation of the Federal strategic plans required by section 403(a) of the Public Health Service Act (42 U.S.C. 283(a)(5)) regarding the conduct and support of research on, and development of, a microbicide to prevent the transmission of the human immunodeficiency virus; and

(2) review and, as appropriate, revise such plan to prioritize funding and activities relative to their scientific urgency and potential market readiness.

UNITED STATES CODE: 42 USC 284

SEC. 106 of P.L. 109-482, NATIONAL INSTITUTES OF HEALTH REFORM ACT OF 2006

ENHANCING THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD (relevant excerpt)

(a) IN GENERAL.—In administering the Clinical and Translational Science Award, the Director of NIH shall establish a mechanism to preserve independent funding and infrastructure for pediatric clinical research centers by—

(1) allowing the appointment of a secondary principal investigator under a single Clinical and Translational Science Award, such that a pediatric principal investigator may be appointed with direct authority over a separate budget and infrastructure for pediatric clinical research; or

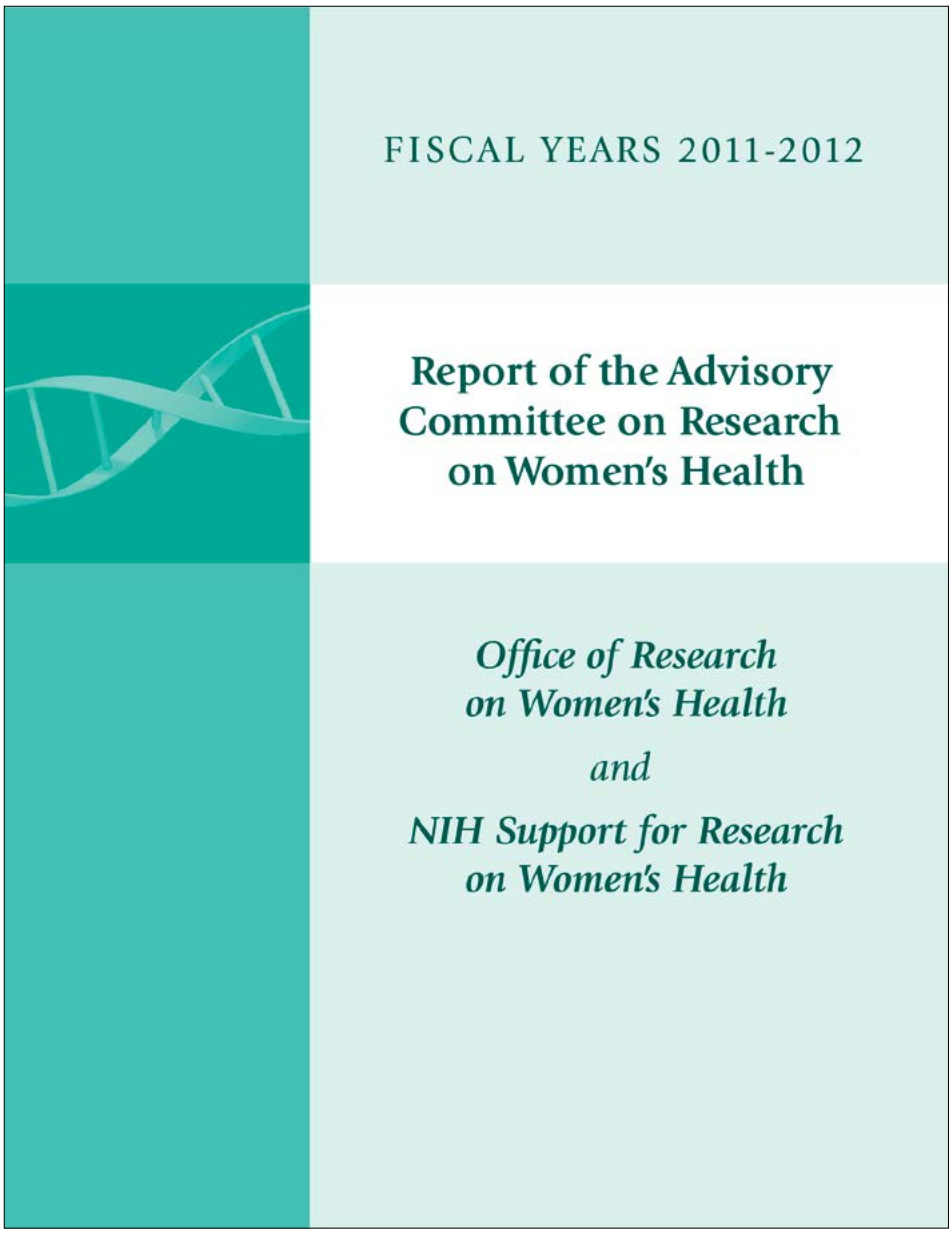
(2) otherwise securing institutional independence of pediatric clinical research centers with respect to finances, infrastructure, resources, and research agenda.

(b) REPORT.—As part of the biennial report under section 403 of the Public Health Service Act, the Director of NIH shall provide an evaluation and comparison of outcomes and effectiveness of training programs under subsection (a).

Appendix B: Report of the Advisory Committee on Research on Women's Health

For the full report, please see:

https://orwh.od.nih.gov/resources/pdf/ACRWH-Biennial-Report2011-2012-Section508Complete.pdf.



Appendix C: Common Fund Strategic Planning Report, 2013

For the full report, please see:

http://commonfund.nih.gov/sites/default/files/Rnd2a_2013_Strategic_Planning_Rept_NIH.pdf.

Appendix D: Priorities and Plans of the ICs and Program Offices in the Office of the Director

This appendix provides links to the current mission statements and strategic plans of the NIH Institutes and Centers (ICs) and the program offices in the Office of the Director. The mission statements and strategic plans presented here classify and justify NIH priorities.

Institutes

National Cancer Institute (NCI)

- Mission Statement: http://www.cancer.gov/aboutnci/overview/mission
- Strategic Plan: https://plan.cancer.gov/

National Eye Institute (NEI)

- Mission Statement: https://nei.nih.gov/about
- Strategic Plan: https://www.nei.nih.gov/strategicplanning/

National Heart, Lung, and Blood Institute (NHLBI)

- Mission Statement: http://www.nhlbi.nih.gov/about/org/mission.htm
- Strategic Plan: https://www.nhlbi.nih.gov/about/documents/strategic-vision

National Human Genome Research Institute (NHGRI)

- Mission Statement: http://www.genome.gov/27534788
- Strategic Plan: https://www.genome.gov/pages/about/planning/2011nhgristrategicplan.pdf

National Institute on Aging (NIA)

- Mission Statement: http://www.nia.nih.gov/about/mission
- Strategic Plan: https://www.nia.nih.gov/about/aging-well-21st-century-strategic-directions-research-aging

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- Mission Statement: http://www.niaaa.nih.gov/about-niaaa
- Strategic Plan: https://www.niaaa.nih.gov/about-niaaa/our-work/strategic-plan

National Institute of Allergy and Infectious Diseases (NIAID)

- Mission Statement: http://www.nih.gov/about/almanac/organization/NIAID.htm
- Strategic Plan: https://www.niaid.nih.gov/about/budget-planning

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

- Mission Statement: http://www.niams.nih.gov/About_Us/Mission_and_Purpose/mission.asp
- Strategic Plan: https://www.niams.nih.gov/About_Us/Mission_and_Purpose/long_range.asp

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

- Mission Statement: https://www.nibib.nih.gov/about-nibib
- Strategic Plan: https://www.nibib.nih.gov/about-nibib/strategic-plan

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- Mission Statement: https://www.nichd.nih.gov/about/overview/mission/pages/index.aspx
- Strategic Plan: https://www.nichd.nih.gov/publications/pubs/Documents/NICHD_scientific_vision120412.pdf

National Institute on Deafness and Other Communication Disorders (NIDCD)

- Mission Statement: https://www.nidcd.nih.gov/about/mission
- Strategic Plan: http://www.nidcd.nih.gov/about/plans/2012-2016/Pages/2012-2016-Strategic-Plan.aspx

National Institute of Dental and Craniofacial Research (NIDCR)

- Mission Statement: http://www.nidcr.nih.gov/AboutUs/MissionandStrategicPlan/MissionStatement/
- Strategic Plan: https://www.nidcr.nih.gov/Research/ResearchPriorities/StrategicPlan/

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- Mission Statement: http://www.nih.gov/about/almanac/organization/NIDDK.htm
- Strategic Plan: https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/Pages/all-reports.aspx

National Institute on Drug Abuse (NIDA)

- Mission Statement: http://www.drugabuse.gov/about-nida
- Strategic Plan: https://www.drugabuse.gov/about-nida/strategic-plan/strategic-plan-workgroup-reports-past-plans

National Institute of Environmental Health Sciences (NIEHS)

- Mission Statement: http://www.niehs.nih.gov/about/index.cfm
- Strategic Plan: https://www.niehs.nih.gov/about/strategicplan/

National Institute of General Medical Sciences (NIGMS)

- Mission Statement: https://www.nigms.nih.gov/about/overview/pages/default.aspx
- Strategic Plan: https://publications.nigms.nih.gov/strategicplan/NIGMS-strategic-plan.pdf

National Institute of Mental Health (NIMH)

- Mission Statement: http://www.nimh.nih.gov/about/index.shtml
- Strategic Plan: https://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml

National Institute on Minority Health and Health Disparities (NIMHD)

- Mission Statement: http://nimhd.nih.gov/about/visionMission.html
- Strategic Plan: https://www.nimhd.nih.gov/about/overview/strategic-plan.html

National Institute of Neurological Disorders and Stroke (NINDS)

- Mission Statement: http://www.ninds.nih.gov/about_ninds/mission.htm
- Strategic Plan: https://www.ninds.nih.gov/About-NINDS/Who-We-Are

National Institute of Nursing Research (NINR)

- Mission Statement: http://www.ninr.nih.gov/AboutNINR/NINRMissionandStrategicPlan/
- Strategic Plan: https://www.ninr.nih.gov/aboutninr/ninr-mission-and-strategic-plan

National Library of Medicine (NLM)

- Mission Statement: http://www.nlm.nih.gov/about/index.html
- Strategic Plan: https://www.nlm.nih.gov/pubs/plan/lrp06/report/default.html

Centers

Center for Information Technology (CIT)

- Mission Statement: http://www.nih.gov/about/almanac/organization/CIT.htm

Center for Scientific Review (CSR)

- Mission Statement: https://public.csr.nih.gov/Pages/default.aspx

John E. Fogarty International Center (FIC)

- Mission Statement: http://www.fic.nih.gov/About/Pages/mission-vision.aspx
- Strategic Plan: https://www.fic.nih.gov/about/pages/strategic-plan.aspx

National Center for Advancing Translational Sciences (NCATS)[786]

- Mission Statement: http://www.ncats.nih.gov/about/about.html

National Center for Complementary and Alternative Medicine (NCCAM)[787]

- Mission Statement: https://nccih.nih.gov/about/ataglance
- Strategic Plan: https://nccih.nih.gov/about/plans

NIH Clinical Center (CC)

- Mission Statement: http://clinicalcenter.nih.gov/about/welcome/mission.shtml
- Strategic Plan: https://clinicalcenter.nih.gov/about/operatingplan.html

[786] On December 23, 2011, President Barack Obama signed the Consolidated Appropriations Act, 2012, which dissolved NCRR and established the National Center for Advancing Translational Sciences (NCATS).

[787] On December 16, 2014, President Barack Obama signed the Consolidated and Further Continuing Appropriations Act, 2015, which changed the name of NCCAM to the National Center for Complementary and Integrative Health (NCCIH). The change was made to more accurately reflect the Center's research commitment to studying promising health approaches that are already in use by the American public. The mission of NCCIH will remains unchanged.

Office of the Director

- Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI): http://dpcpsi.nih.gov/about.aspx
- Office of Extramural Research (OER): http://grants.nih.gov/grants/intro2oer.htm
- Office of Intramural Research (OIR): http://sourcebook.od.nih.gov/about/leadership-staff
- Office of Management: http://om.od.nih.gov/vision.html
- Office of Science Policy: http://osp.od.nih.gov/
- Office of Communications and Public Liaison (OCPL): http://www.nih.gov/icd/od/ocpl/mission.htm
- Office of Equity, Diversity, and Inclusion: https://www.edi.nih.gov/
- Office of Legislative Policy and Analysis: http://olpa.od.nih.gov/about/mission/default.asp
- Office of the Ombudsman/Center for Cooperative Resolution: https://ombudsman.nih.gov/
- NIH Ethics Program: http://ethics.od.nih.gov/overview.htm
- Office of the Chief Information Officer: https://ocio.nih.gov/aboutus/Pages/default.aspx

Appendix E: Research Training and Graduate Medical Education Data

National Research Service Award (NRSA) and National Library of Medicine Research Training Programs: Ph.D. Recipients by Field of Study[788]

Field of Study	FY 2012	FY 2013
Life Sciences	2,663	2,644
Biological/Biomedical Sciences	**2,399**	**2,352**
Anatomy	5	4
Bacteriology	5	7
Biochemistry	180	161
Bioinformatics	29	38
Biology/Biomedical Sciences, General	42	51
Biology/Biomedical Sciences, Other	13	22
Biomedical Sciences	85	114
Biometrics and Biostatistics	43	32
Biophysics	57	53
Biotechnology	5	4
Botany/Plant Biology	8	2
Cancer Biology	123	103
Cell/Cellular Biology and Histology	138	124
Computational Biology	17	30
Developmental Biology/Embryology	77	75
Ecology	5	5
Endocrinology	7	11
Entomology	3	2
Evolutionary Biology	15	14
Genetics/Genomics, Human and Animal	120	157
Immunology	216	214
Microbiology	138	120

[788] Source: Data are drawn from NIH Trainee and Fellow File, IMPAC II, and the Doctorate Records File on 2/27/2015 and are subject to change.

Field of Study	FY 2012	FY 2013
Molecular Biology	169	190
Neurosciences	509	472
Nutritional Sciences	35	20
Parasitology	10	9
Pathology, Human and Animal	42	38
Pharmacology, Human and Animal	107	106
Physiology, Human and Animal	72	51
Plant Genetics	4	3
Plant Pathology/Phytopathology	1	1
Plant Physiology	1	0
Structural Biology	14	21
Toxicology	35	43
Virology	66	55
Zoology	3	0
Health Sciences	**257**	**283**
Environmental Health	9	11
Environmental Toxicology	0	0
Epidemiology	69	79
Gerontology	4	0
Health Sciences, General	5	6
Health Sciences, Other	4	8
Health Systems/Services Administration	1	6
Kinesiology/Exercise Science	9	3
Medicinal/Pharmaceutical Sciences	27	24
Nursing Science	61	58
Oral Biology/Oral Pathology	4	4
Public Health	43	52
Rehabilitation/Therapeutic Services	7	8
Speech-Language Pathology and Audiology	10	18
Veterinary Sciences	4	6

Field of Study	FY 2012	FY 2013
Agricultural Sciences/Natural Resources	**7**	**9**
Agriculture, General	0	0
Animal Science, Other	3	0
Environmental Science	0	4
Fishing and Fisheries Sciences/Management	1	0
Food Science	0	1
Food Sciences and Technology, Other	0	1
Forest Sciences and Biology	0	1
Natural Resources/Conservation	1	0
Plant Pathology/Phytopathology	1	0
Plant Sciences, Other	1	2
Soil Chemistry/Microbiology	0	0
Soil Sciences, Other	0	0
Social Sciences	257	284
Psychology	**195**	**215**
Clinical Psychology	79	95
Cognitive Psychology and Psycholinguistics	24	20
Counseling	1	3
Developmental and Child Psychology	19	22
Educational Psychology	1	0
Experimental Psychology	9	13
Family Psychology	0	0
Human Development and Family Studies	4	12
Industrial and Organizational Psychology	1	0
Personality Psychology	0	1
Physiological/Psychobiology	16	19
Psychology, General	10	11
Psychology, Other	8	5
Psychometrics and Quantitative Psychology	4	4
School Psychology	1	0

Field of Study	FY 2012	FY 2013
Social Psychology	18	10
Social Sciences	**62**	**69**
Anthropology	6	7
Area/Ethnic/Cultural/Gender Studies	0	0
Criminal Justice and Corrections	0	0
Criminology	0	0
Demography/Population Studies	8	3
Econometrics	1	0
Economics	11	12
Geography	3	0
International Relations/Affairs	1	0
Linguistics	1	3
Political Science and Government	2	0
Public Policy Analysis	4	7
Social Sciences, General	2	2
Social Sciences, Other	0	7
Sociology	22	28
Statistics	1	0
Physical Sciences	161	147
Chemistry	**83**	**82**
Analytical Chemistry	11	12
Chemistry, General	7	5
Chemistry, Other	15	20
Inorganic Chemistry	8	7
Organic Chemistry	29	34
Physical Chemistry	10	4
Polymer Chemistry	0	0
Theoretical Chemistry	3	0
Computer Sciences	**14**	**11**
Computer and Information Science, Other	1	1
Computer Science	9	9

Field of Study	FY 2012	FY 2013
Information Science and Systems	2	1
Robotics	2	0
Mathematics	**22**	**17**
Analysis and Functional Analysis	0	0
Applied Mathematics	3	5
Geometry/Geometric Analysis	0	1
Mathematics/Statistics, General	2	0
Mathematics/Statistics, Other	2	0
Number Theory	0	1
Statistics	15	10
Other Physical Sciences	**2**	**3**
Atmospheric Chemistry and Climatology	0	1
Atmospheric Science/Meteorology, General	0	0
Hydrology and Water Resources	1	0
Marine Sciences	0	1
Oceanography, Chemical and Physical	1	1
Physics	**40**	**34**
Applied Physics	0	1
Atomic/Molecular/Chemical Physics	0	0
Biophysics	19	12
Condensed-Matter/Low-Temperature Physics	0	1
Medical Physics/Radiological Science	17	13
Nuclear Physics	0	1
Optics/Phototonics	3	1
Particle (Elementary) Physics	0	0
Physics, General	1	2
Physics, Other	0	3
Plasma/Fusion Physics	0	0
Engineering	**230**	**222**
Aerospace, Aeronautical and Astronautical	1	0
Agricultural	0	1

Field of Study	FY 2012	FY 2013
Bioengineering and Biomedical	181	179
Chemical	21	22
Civil	1	0
Communications	0	1
Computer	1	0
Electrical, Electronics and Communications	6	6
Engineering Mechanics	0	0
Engineering, Other	4	1
Environmental Health Engineering	1	1
Industrial and Manufacturing	1	0
Materials Science	5	4
Mechanical	5	4
Operations Research	0	0
Polymer and Plastics	1	0
Systems	2	3
Education	6	10
Humanities	3	8
Other Fields	11	24
TOTAL	3,331	3,339

Demographic Characteristics of NRSA Participants[789]

Characteristic	FY 2012, %	FY 2013, %
Gender		
Female	53.1	52.7
Male	45.1	44.9
Unknown	0.4	1.4
Withheld	1.4	1.0
Race		
White	66.2	65.6

[789] Source: Data are drawn from IMPAC II Current Files and Doctorate Records File as of 2/27/2015 and are subject to change. For individuals whose Race or Ethnicity was Unknown or Withheld, IMPAC II data were supplemented with information from the Doctorate Records File.

Characteristic	FY 2012, %	FY 2013, %
Asian	15.3	15.3
African American	6.8	6.7
Native American	0.4	0.4
Native Hawaiian/Pacific Islander	0.2	0.2
Multiple Races (including more than one race)	3.4	3.9
Withheld	6.7	7.3
Unknown	0.9	0.7
Ethnicity		
Hispanic	9.5	10.2
Non-Hispanic	83.8	82.9
Unknown	2.5	1.6
Withheld	4.3	5.4

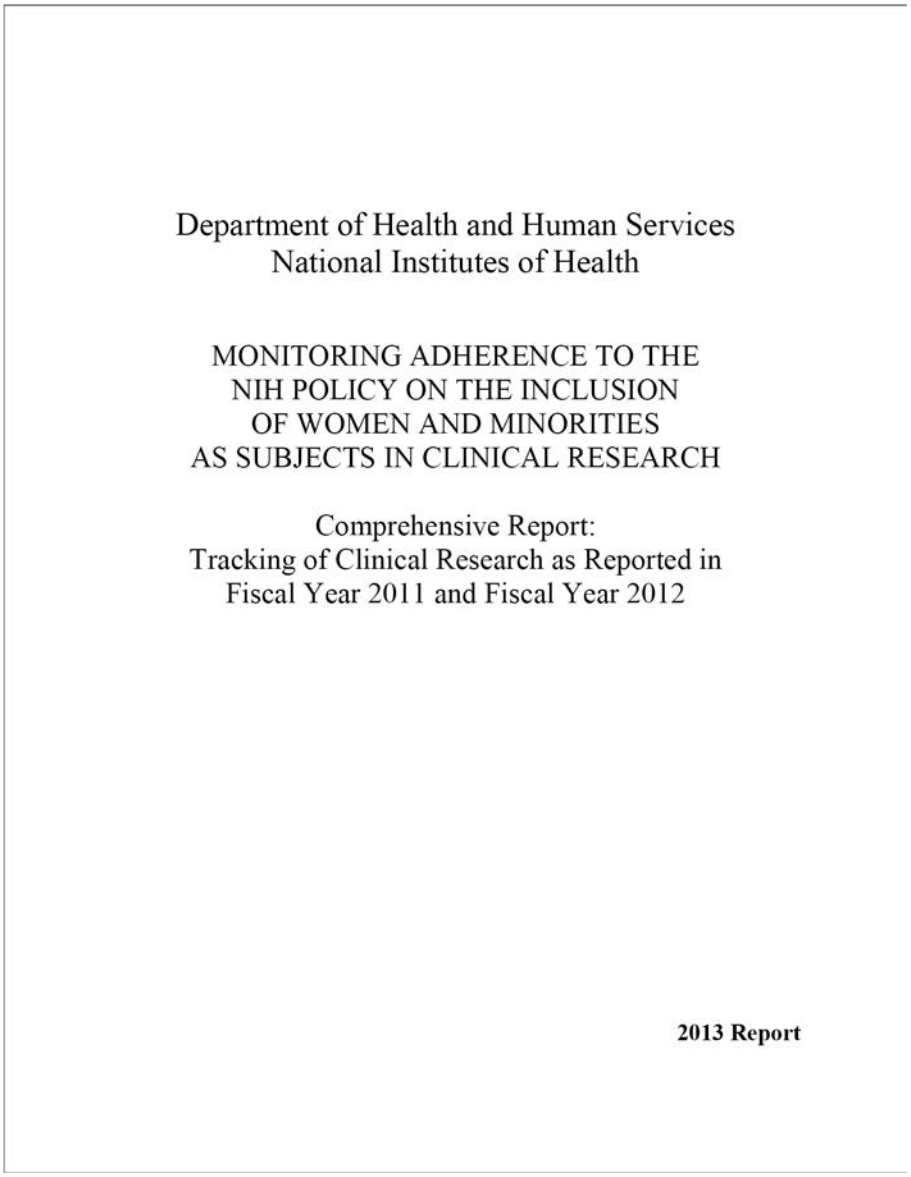
Successfully Completed Residency and Subspecialty Training by Academic Year

NIH Clinical Center Program Specialty	Successfully Completed 2011/2012	2012/2013
Allergy and Immunology	3	3
Medical Genetics	2	4
Medical Biochemical Genetics	1	2
Critical Care Medicine	1	5
Endocrinology, Diabetes, and Metabolism	5	5
Hematology	4	4
Infectious Disease	5	5
Oncology	12	8
Rheumatology	3	3
Pathology — Anatomic and Clinical	3	3
Blood Banking/Transfusion Medicine	2	2
Cytopathology	1	1
Hematology (Pathology)	2	2
Pediatric Endocrinology	2	2
Psychiatry	3	1
Vascular Neurology	1	2
Hospice and Palliative Medicine	1	1
Neurological Surgery (new program)	0	0
Total	45	47

Appendix F: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

For the full report, please see:

http://orwh.od.nih.gov/research/inclusion/reports.asp.



Department of Health and Human Services
National Institutes of Health

MONITORING ADHERENCE TO THE
NIH POLICY ON THE INCLUSION
OF WOMEN AND MINORITIES
AS SUBJECTS IN CLINICAL RESEARCH

Comprehensive Report:
Tracking of Clinical Research as Reported in
Fiscal Year 2011 and Fiscal Year 2012

2013 Report

Appendix G: Catalog of Disease Registries, Databases, and Biomedical Information Systems

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
3D Atlas & Database of Murine Urogenital Development	NIDDK	NIDDK	Medical Research Council
3D Slicer Registration Case Library	NIBIB	NINDS, NHLBI, OD/OSC (Common Fund)	Brigham and Women's Hospital
3D Swarms	NIAID	NIAID	NIAID
A Platform for Modeling the Global Impact of Climate Change on Infectious Disease	NLM	NLM	Children's Hospital Corporation
A Unified Clinical Genomics Database	NHGRI	NHGRI, NICHD	Brigham and Women's Hospital
ABC-GENES PORTAL	NCI	NCI	NCI
Action for Health in Diabetes (LookAHEAD) and follow-up study	NIDDK	NIDDK	Wake Forest School of Medicine and DCC
Active Patient Participation in a Disease Registry for Comparative Effectiveness	NLM	NLM	Children's Hospital Corporation
Acute liver failure registry in the Acute Liver Failure Study Group (ALFSG)	NIDDK	NIDDK	University of Texas Southwestern Medical Center and DCC
AFINITI: An Augmented System for Neuroimaging Followup	NLM	NLM	Methodist Hospital Research Institute
AIDSinfo / infoSIDA	NLM	NLM, NIAID, OD/OAR	NLM
Alcohol Policy Information System (APIS)	NIAAA	NIAAA	CDM Group, Inc.
ALTBIB: Resources for Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing	NLM	NLM	NLM
Alzheimer's Disease Neuroimaging Initiative (ADNI)	NIA	NCRR, NIA, NIMH, NINDS, NINR	University of California, San Francisco
Alzheimer's Disease Patient Registry (ADPR)	NIA	NIA	Group Health Cooperative and Mayo Clinic College of Medicine, Rochester
American Time Use Survey Well-Being Module	NIA	NIA	Bureau of Labor Statistics

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
Analysis and Annotation of the *E. coli* Genome Sequence	NIGMS	NIGMS	University of Miami School of Medicine
AphasiaBank: A Shared Database for the Study of	NIDCD	NIDCD	Carnegie-Mellon University
Asia Pacific HIV Observational Database (APHOD)	NIAID	NIAID, NCI, NICHD	Foundation for AIDS Research
Aspergillus Genome Database	NIAID	NIAID,	Stanford University
Asthma Birth Cohorts Database	NIAID	NIAID	NIAID
Audiological and Genetic Resource for Pediatric Hearing Research	NIDCD	NIDCD	Children's Hospital of Philadelphia
Autism Genetic Resource Exchange (AGRE)	NIMH	NIMH, NICHD	Autism Speaks, Inc.
Automated Detection of Anomalous Accesses to Electronic Health Records	NLM	NLM	Vanderbilt University
Baseline Microdata for Analysis of U.S. Demographic Change	NICHD	NICHD	University of Minnesota Twin Cities
Belarus Tuberculosis Portal	NIAID	NIAID	NIAID
Beta Cell Biology Consortium (BCBC)	NIDDK	NIDDK	Vanderbilt Medical Center and CC
BioGRID: An Open Integrated Resource for Biological Interaction Data	OD/ORIP	OD/ORIP	MT Sinai Hospital-Samuel Lunenfeld Research Institute
Biological Biochemical Image Database (BBID)	NIA	NIA	NIA
Biological Magnetic Resonance Data Bank	NLM	NLM	University of Wisconsin Madison
Biological Specimen and Data Repositories Information Coordinating Center (BioLINCC)	NHLBI	NHLBI	Information Management Services, Inc.
Biomedical Informatics Research Network (BIRN) Data Repository	NCRR	NCRR	University of California, San Diego
Biomedical Translational Research Information System (BTRIS)	CC	CC	NIH Clinical Center
Biospecimen Research Database	NCI	NCI	NCI
Blueprint Neurotherapeutics Database	NINDS	NINDS	Collaborative Drug Discovery, Inc.
Boston Area Community Health (BACH) III Survey	NIDDK	NIDDK	New England Research Institutes, Inc.
BrainSpan: Atlas of the Developing Human Brain	NIMH	NIMH, NINDS, NIDA	Allen Brain Institute, Yale University, and University of Southern California
Breast and Colon Cancer Family Registries	NCI	NCI	Multiple
Breast Cancer Information Core (BIC)	NHGRI	NHGRI	NHGRI
Breast Cancer Surveillance Consortium	NCI	NCI	Multiple
caArray	NCI	NCI	NCI

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
caBIG Enterprise	NCI	NCI	NCI
CADD Group Chemoinformatics Tools and User Services	NCI	NCI	NCI
caIntegrator	NCI	NCI	NCI
California Health Interview Survey	NCI	NCI	UCLA Center for Health Policy Research External Web Site Policy, California Department of Public Health, and California Department of Health Care Services
caMOD	NCI	NCI	NCI
Cancer Control P.L.A.N.E.T.	NCI	NCI	NCI
Cancer Data Access System (CDAS) for PLCO and NLST	NCI	NCI	NCI
Cancer Genetics Network	NCI	NCI	Massachusetts General Hospital
Cancer Genome Anatomy Project (CGAP)	NCI	NCI	NCI
Cancer Intervention and Surveillance Modeling Network (CISNET)	NCI	NCI	NCI
cancer Nanotechnology Laboratory (caNanoLab)	NCI	NCI	NCI
Cancer Prevalence and Cost of Care Projections	NCI	NCI	NCI
Cancer Research Network	NCI	NCI	NCI
Cancer Survivor Prevalence Data	NCI	NCI	NCI
Cancer Trends Progress Report	NCI	NCI	NCI
Candida Genome Database	NIDCR	NIDCR, NIAID	Stanford University
Carcinogenic Potency Database (CPDB)	NLM	NLM	NLM and University of California, Berkeley Lawrence Berkeley National Laboratory
CardioVascular Research Grid (CVRG)	NHLBI	NHLBI	Johns Hopkins University
Catalog of microRNA eQTLs	NHLBI	NHLBI, NLM	NHLBI
CCASAnet: Caribbean, Central and South America Network	NIAID	NIAID	Vanderbilt University School of Medicine
CDC Dental, Oral, and Craniofacial Data Resource Center	NIDCR	NIDCR, CDC	NIDCR, CDC
Center for International Blood and Marrow Transplant Research (CIBMTR)	NCI	NCI, NHLBI, NIAID	Medical College of Wisconsin and National Marrow Donor Program
Center for Zebrafish CHromatin and Epigenetics (CZECH)	NICHD	NICHD	University of Utah
Chemical Effects in Biological Systems	NIEHS	NIEHS	NIEHS
Chemical Hazards Emergency Medical Management (CHEMM)	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
ChemIDplus	NLM	NLM	NLM
Chest x-ray image dataset	NLM	NLM	Indiana University
Childhood Liver Disease Research and Education Network (ChiLDREN)	NIDDK	NIDDK	University of Michigan and DCC
China Health and Retirement Longitudinal Study (CHARLS)	NIA	NIA	Peking University
Classification of Laws Associated with School Students (CLASS)	NCI	NCI	NCI
Clinical Research Study Investigator's Toolbox	NIA	NIA	NIA
Clinical Sequencing Exploratory Research (CSER) Coordinating Center	NHGRI	NHGRI	University of Washington
Clinical Trials Network Dissemination Library	NIDA	NIDA	Washington University
Clinical trials public data share website	NIDA	NIDA	EMMES Corporation
ClinicalTrials.gov	NLM	NLM	NLM
ClinVar	NLM	NLM	NLM
Clone DB	NLM	NLM	NLM
Clusters of Orthologous Groups (COGS)	NLM	NLM	NLM
Collaborative Health Outcomes Information Registry (CHOIR)	NIDA	NIDA, NIA, ORWH, NINR, NEI, NCCAM, NINDS	Stanford Medical School
Collaborative Islet Transplant Registry (CITR)	NIDDK	NIDDK	EMMES Corporation
Collaborative Studies on Genetics of Alcoholism (COGA) database	NIAAA	NIAAA	SUNY Downstate Medical Center
Colorectal Cancer Mortality Projections	NCI	NCI	NCI
Combining Medications and Behavioral Interventions (COMBINE) data set	NIAAA	NIAAA	NIAAA
Comparative RNA Web Site (CRW) Project: A Comparative Database of RNA Molecules	NIGMS	NIGMS	University of Texas Austin
Comparative Toxicogenomics Database (CTD)	NIEHS	NIEHS/NLM	Mount Desert Island Biological Lab
Comprehensive Database of Drug Discrimination and Self-Administration Research	NIDA	NIDA	King's College London and University of Texas Health Science Center, Houston
Computational Genotyping System for Improved Influenza Surveillance	NLM	NLM	University of Nebraska Omaha
Computer Access to Research on Dietary Supplements (CARDS) database	OD/ODS	OD/ODS	OD/ODS
Computer-assisted functional neurosurgery	NIBIB	NIBIB	Vanderbilt University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
Consensus Coding Sequence (CCDS) database	NLM	NLM	NLM
Conserved Domains Database (CDD)	NLM	NLM	NLM
Consortium on Interplay of Genes and Environment across Multiple Studies	NIA	NIA	
Coordinating and Bioinformatics Unit for the DCC/MMPC (Diabetic Complications Consortium/Mouse Metabolic Phenotyping Centers)	NIDDK	NIDDK	Augusta University
Copy Number Variation (CNV) Atlas of Human Development	OD	NICHD	Emory University
CPTAC antibody portal	NCI	NCI	Leidos
CPTAC Data Portal	NCI	NCI	ESAC
CRCNS Data Sharing: NeuroML Database for Multiscale Neuroscience Models	NIBIB	NIBIB	Arizona State University-Tempe
Creating a Biomarker Registry for Secondary Data Collections	NIA	NIA, NICHD, NLM	University of Michigan at Ann Arbor
Creating a Developmental Gene Expression Atlas for Rhesus Macaque Brain	NIMH	NINDS, NIMH	Allen Institute for Brain Science
DailyMed	NLM	NLM	NLM
Data Management and Coordinating Center (DMCC)	NINDS	NCATS	University of South Florida
Database for Annotation, Visualization, and Integrated Discovery (DAVID)	NIAID	NIAID	NIAID
Database for Modified Nucleotides, Fluorophors, and Additives	NIGMS	NIGMS	DNA Software, Inc.
Database of expressed sequence tag records (dbEST)	NLM	NLM	NLM
Database of Functional SNPs in Cancer-Related Environmentally Responsive Genes	NCI	NCI, NIEHS	Yale University
Database of Genome Survey Sequences (dbGSS)	NLM	NLM	NLM
Database of Genomic Structural Variation (dbVar)	NLM	NLM	NLM
Database of Genotypes and Phenotypes (dbGaP)	NLM	NLM	NLM
Database of Interacting Proteins (DIP)	NIGMS	NIGMS	University of California, Los Angeles
Database of longitudinal studies	NIA	NIA	NIA
Database of major histocompatibility complex (dbMHC)	NLM	NLM	NLM
Database of Short Genetic Variations (dbSNP)	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
Decision Support System for Temporal Lobe Epilepsy	NIBIB	NIBIB	Henry Ford Health System
Development of a National Incompatible Kidney Transplant Registry	NIDDK	NIDDK, NLM, OD	Johns Hopkins University
Development of a Pediatric Myelodysplastic Syndrome Patient Registry	NIDDK	NIDDK	Children's Hospital Corporation, Boston
Development of a Research-Ready Pregnancy and Newborn Biobank in California	NICHD	NICHD	Sequoia Foundation
Development of a Web-based Data Retrieval System for HIV Therapy Guidance	NIAID	NIAID	Monogram Biosciences, Inc.
Development of an Infertility Family Registry (IFRR)	NICHD	NICHD	Dartmouth College
Development of dictyBase, an online informatics resource	NIGMS	NIGMS	Northwestern University
Development of NIAAA Correlational Database	NIAAA	NIAAA	Genome Exploration, Inc.
Developmental and Reproductive Toxicology Database (DART)	NLM	NLM	NLM
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)	NIDDK	NIDDK	NIDDK and DCC
Diabetes Prevention Program Outcomes Study (DPPOS)	NIDDK	NIDDK	George Washington University and DCC
Diazeniumdiolate Database	NCI	NCI	NCI
Dietary Supplement Ingredient Database	OD/ODS	OD/ODS, FDA, CDC, NIST	OD/ODS
Dietary Supplement Label Database	NLM	ODS, NLM	ODS
Digitized Atlas of Mouse Liver Lesions	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
Directory of Health Organizations Online (DIRLINE)	NLM	NLM	NLM
Disaster Lit: Resource Guide for Disaster Medicine and Public Health	NLM	NLM	NLM
Disorders of Sex Development network patient registry	NICHD	NICHD	UCLA
Division of AIDS (DAIDS) Anti-HIV/OI/TB Therapeutics Database	NIAID	NIAID	Gryphon Scientific LLC
DNA Polymerase Database	NIGMS	NIGMS	New England Biolabs, Inc.
Drug-Induced Liver Injury Network (DILIN) retrospective study (ILIAD)	NIDDK	NIDDK	Duke University and DCC
DrugMatrix	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
DS-Connect™: The Down Syndrome Registry	NICHD	NICHD	NIH

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Early Detection Research Network (EDRN)	NCI	NCI	Multiple
East Africa International Epidemiology Databases to Evaluate AIDS (IeDEA) Regional Consortium	NIAID	NIAID	Indiana University
East African Network for Informatics Training/AMPATH Medical Record System (AMRS)	FIC	FIC, NHGRI	Regenstrief Institute
EcoCyc model organism database for *Escherichia coli*	NIGMS	NIGMS	SRI International
EcoliHub2.0: A Next-Generation *E. coli* Model Organism Resource	NIGMS	NIGMS	University of Southern California
EM Open Connectome Project	NIBIB	NIBIB	Johns Hopkins University (subcontract to Harvard)
eMERGE Network Coordinating Center	NHGRI	NHGRI, OD	Vanderbilt University Medical Center
ENCODE Data Analysis Center (EDAC)	NHGRI	NHGRI	University of Massachusetts Medical School, Worcester
ENCODE Data Coordinating Center	NHGRI	NHGRI	Stanford University
English Longitudinal Study of Ageing	NIA	NIA	University College London
Environmental Polymorphisms Registry (EPR)	NIEHS/NCRR	NIEHS/NCRR	Integrated Laboratory Systems, Inc., and University of North Carolina
Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)	OER	OD	NIH
Eukaryotic Pathogen Database Resources (EuPathDB)	NIAID	NIAID	University of Pennsylvania
Exploratory Evaluation of Homomorphic Cryptography For Confidentiality Protection	NLM	NLM	BioMedware
FaceBase: a resource for craniofacial researchers	NIDCR	NIDCR	University of Iowa and University of Pittsburgh
Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System	NINDS	NINDS, DoD	NIH CIT
Finding Cancer Statistics	NCI	NCI	NCI
FLYBASE: a Drosophila genomic and genetic database	NHGRI	NHGRI	Harvard University
Food Attitudes and Behaviors Survey	NCI	NCI	NCI
Gastroparesis Registry 2: Gastroparesis Clinical Research Consortium (GpCRC)	NIDDK	NIDDK	Johns Hopkins University and DCC
Gateway to Global Aging Data	NIA	NIA	University of Southern California
Geisha: A Chicken Embryo Gene Expression Resource	NICHD	NICHD	University of Arizona

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
GenBank	NLM	NLM	NLM
GENCODE: comprehensive gene annotation for human and mouse	NHGRI	NHGRI	Sanger Institute
Gene Expression Nervous System Atlas (GENSAT)	NINDS, NLM	NINDS, NLM	Rockefeller University and NLM
Gene Expression Omnibus (GEO)	NLM	NLM	NLM
GeneNetwork	NIAAA	NIAAA	University of Tennessee Health Sciences Center
Genetic and Rare Diseases Information Center (GARD)	NCATS	NHGRI	ICFI
Genetic Association Database	NIA, CIT	NIA, CIT	National Institutes of Health
Genetic Testing Registry (GTR)	NLM	NLM, OD	NLM
Genetic Toxicology Data Bank (GENE-TOX)	NLM	NLM	EPA
Genetics Home Reference	NLM	NLM	NLM
GenitoUrinary Development Molecular Anatomy Project (GUDMAP)	NIDDK, NICHD	NIDDK, NICHD	University of Southern California and coordinator
Genomic Datasets for Cancer Research	NCI	NCI	NCI
Genomics and bioinformatics software tools	NCI	NCI	NCI
Geographic Information System for Breast Cancer Studies on Long Island	NCI	NCI	Multiple
Global Rare Diseases Patient Registry Data Repository (GRDR®)	NCATS	NCATS	NCATS
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)	NIDDK	NIDDK	George Washington University and DCC
Grid-Enabled Measures Database	NCI	NCI	NCI
H3ABioNet: A Sustainable African Bioinformatics Network for H3Africa	NHGRI	NHGRI, OD	University of Cape Town
Haz-Map: Information on Hazardous Chemicals and Occupational Diseases	NLM	NLM	NLM
Hazardous Substances Data Bank (HSDB)	NLM	NLM	NLM
Health and Retirement Study	NIA	NIA	University of Michigan
Health Disparities Calculator (HD*Calc)	NCI	NCI	NCI
Health Hotlines	NLM	NLM	NLM
Health Information National Trends Survey	NCI	NCI	NCI
Health Services and Sciences Research Resources (HSRR)	NLM	NLM	NLM
Health Services Research Projects in Progress (HSRProj) database	NLM	NLM	NLM

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Health Services/Technology Assessment Text (HSTAT)	NLM	NLM	NLM
HealthReach	NLM	NLM	NLM
Hemagglutinin Structure Prediction Server (HASP)	NIAID	NIAID	NIAID
Hepatitis B Research Network: observational databases in adults and children	NIDDK	NIDDK	University of Pittsburgh and DCC
Hereditary Causes of Nephrolithiasis and Kidney Failure	NIDDK	NIDDK	Mayo Clinic Rochester
Histone Sequence Database	NHGRI	NHGRI, NLM	NHGRI, NLM
HIV Drug Resistance Database	NIAID	NIAID	Stanford University
HIV Molecular Immunology Database	NIAID	DoE, NIAID	Los Alamos National Laboratory
HIV Sequence Database	NIAID	DoE, NIAID	Los Alamos National Laboratory
HIV-1 Human Interaction Database	NLM	NIAID, NLM	NLM
HIV-1 resistance mutation database	NIAID	DoE, NIAID	Los Alamos National Laboratory
HIV-1/SIV Antibody Neutralization Assay Improvements and Database Development	NIAID	NIAID	Monogram Biosciences, Inc.
HIV/SIV Database and Analysis Unit	NIAID	NIAID	NIAID
HomoloGene	NLM	NLM	NLM
Household Products Database	NLM	NLM	NLM
Human “Brain Bank” Tissue for Alcohol Research	NIAAA	NIAAA	University of Sydney
Human Biological Data Interchange	NIDDK	NIDDK	National Disease Research Interchange (NIDDK and others)
Human Islet Research Network (HIRN)	NIDDK	NIDDK	Beckman Research Institute of the City of Hope and CC
Human Nutrition Research and Information Management (HNRIM) database	NIDDK	NIDDK	NIDDK
Human Oral Microbiome Database (HOMD)	NIDCR	NIDCR	The Forsyth Institute
IGNITE Coordinating Center	NHGRI	NHGRI	University of Pennsylvania
Images from the NLM	NLM	NLM	NLM
ImmPort	NIAID	NIAID	Northrup Grummon
Immune Epitope Database and Analysis Program	NIAID	NIAID	La Jolla Institute for Allergy & Immunology
Immune Polymorphism Database/ major histocompatibility complex of non-human primates	NIAID	NIAID	European Molecular Biology Laboratory/European Bioinformatics Institute
ImmuneSpace: Human Immunology Project Consortium (HIPC) database	NIAID	NIAID	Fred Hutchinson Cancer Research Center
Inferred Biomolecular Interaction Server (IBIS)	NLM	NLM	NLM

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Influenza Research Database	NIAID	NIAID	Northrup Grumman Health IT, J. Craig Venter Institute
Influenza Virus Resource	NLM	NLM	NLM
Informatics for Integrating Biology and the Bedside (i2b2)	NIMHD	NIMHD	Jackson State University; University of Puerto Rico, Medical Science Campus; and Morehouse School of Medicine
Inherited Bone Marrow Failure Syndromes	NCI	NCI	NCI
Instruments to Detect Cognitive Impairment in Older Adults	NIA	NIA	NIA
Integrated Risk Information System (IRIS)	NLM	NLM, EPA	NLM
Integrating Data, Models, and Reasoning in Critical Care	NIBIB	NIBIB	Massachusetts Institute of Technology
Integrative Analysis of Longitudinal Studies of Aging	NIA	NIA	Oregon Health Sciences University
Interagency Registry for Mechanically Assisted Circulatory Support	NHLBI	NHLBI	University of Alabama at Birmingham
International Cancer Research Partnership	NCI	NCI	NCI
International Epidemiologic Databases to Evaluate AIDS (IeDEA) in Central Africa (Region 9)	NIAID	NIAID, NCI, NICHD	Research Triangle Institute
International Epilepsy Electrophysiology Database	NINDS	NINDS	University of Pennsylvania
International Myositis Assessment & Clinical Studies Group (IMACS) Outcomes Repository	NIEHS	NIEHS	NIEHS
International Network and Registry for Thrombotic Microangiopathy (TMA)	NIDDK	NIDDK	Feinstein Institute for Medical Research
International Registry of Werner Syndrome	NCI	NCI, NIA	University of Washington
International Research Registry Network for Sjögren's Syndrome	NIDCR	NIDCR, NEI	University of California, San Francisco
International Skeletal Dysplasia Registry	NICHD	NICHD	Cedars-Sinai Medical Center
International Toxicity Estimates for Risk (ITER)	NLM	NLM	TERA
Irish Longitudinal Study on Ageing	NIA	NIA	Trinity College, Dublin
Japanese Study of Ageing and Retirement	NIA	NIA	Research Institute of Economy, Trade, and Industry; Hitotsubashi University; and University of Tokyo
Kaiser Permanente Autoimmune Disease Registry	NIAID	NIAID, NIDDK, OD	Kaiser Foundation Research Institute

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Korean Longitudinal Study of Ageing	NIA	NIA	Korea Labor Institute
Laboratory of Neural Imaging (LONI) Image Data Archive	NIBIB	NIBIB	University of California, Los Angeles
LactMed: drugs and lactation database	NLM	NLM	NLM
Legacy Informatics Resources for Glycomics	NIGMS	NIGMS	Massachusetts Institute of Technology
Library of Integrated Network-based Cellular Signatures (LINCS)	NHLBI/NHGRI	OD/OSC (Common Fund)	Multiple
Li-Fraumeni Syndrome Study	NCI	NCI	NCI
Limited Access Datasets from NIMH Clinical Trials	NIMH	NIMH	NIMH
LiverTox: database of clinical and research information on drug-induced liver injury	NIDDK, NLM	NIDDK, NLM	NIDDK, NLM
Longitudinal Ageing Study in India	NIA	NIA	Harvard School of Public Health
Longitudinal Assessment of Bariatric Surgery (LABS)	NIDDK	NIDDK	University of Pittsburgh and DDC
Malaria Research Resources	NLM	NLM	NLM
MetaCyc & BioCyc Pathway/Genome Databases	NIGMS	NIGMS	SRI International
MEthotrexate Response In Treatment of Ulcerative Colitis (MERIT-UC) Trial	NIDDK	NIDDK	University of North Carolina at Chapel Hill
Mexican Health and Aging Study	NIA	NIA	Universities of Pennsylvania, Maryland, and Wisconsin in the U.S., and the Instituto Nacional de Estadística, Geografía e Informática (INEGI) in Mexico
Micro-Manager	NIBIB	NIBIB	University of California, San Francisco
Midlife in the United States	NIA	NIA	University of Wisconsin
Molecular Imaging and Contrast Agent Database (MICAD)	NCI, NLM	CF	NLM
Molecular Modeling Database (MMDB)	NLM	NLM	NLM
Monitoring the Future (MTF)	NIDA	NIDA	University of Michigan
Monkey Cortical Connections Database	NIMH	NIMH, NIA, NIAAA, NIBIB, NICHD, NIDA, NINDS, NLM	University of California, Davis
Morehouse Healthcare Personalized Health for Women (P4)	NIMHD	NIMHD	Morehouse School of Medicine
Mouse Gene Expression Database	NICHD	NICHD	Jackson Laboratory
Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network	NIDDK	NIDDK	Multiple (University of Pennsylvania, DCC)
Multiscale Framework for Molecular Heterogeneity Analysis	NLM	NLM	Emory University

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Mutant Mouse Resource and Research Centers Informatics, Coordination, and Service Center	OD/ORIP	OD/ORIP	University of California, Davis
Nanomaterial Registry	NIBIB	NIEHS, NCI	RTI International
National Addiction & HIV Data Archive Program	NIDA	NIDA	University of Michigan
National Alzheimer's Coordinating Center (NACC)	NIA	NIA	University of Washington
National Archive of Computerized Data on Aging (NACDA)	NIA		ICPSR
National Biomedical Imaging Archive (NBIA)	NCI	NCI	NCI
National Database for Autism Research (NDAR)	NIMH	NIMH	NIMH
National Endoscopic Database of the Clinical Outcomes Research Initiative	NIDDK	NIDDK	Oregon Health & Science University
National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	NIAAA	NIAAA	NIAAA
National Health and Aging Trends Study (NHATS)	NIA	NIA	Johns Hopkins University
National Health and Nutrition Examination Survey (NHANES)	NCI	multiple	National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC)
National Health Interview Survey (NHIS) (CDC)	NCCAM	NCCAM	
National Health Interview Survey (NHIS) Cancer Control Supplement	NCI	NCI, CDC	National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC)
National Long Term Care Survey (NLTCS)	NIA	NIA	Duke University
National Longitudinal Alcohol Epidemiologic Survey (NLAES)	NIAAA	NIAAA	NIAAA
National NeuroAIDS Tissue Consortium	NIMH	NIMH, NINDS	University of Texas Medical Branch; University of California, San Diego; Reed Neurological Research Center; Mount Sinai Medical Center; EMMES Corporation; and University of Nebraska
National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE)	NEI	NEI	NEI
National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy patients and family members	NHLBI	NINDS	University of Rochester

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National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)	NHLBI	NHLBI, NIAMS	RTI International
National Social Life, Health, and Aging Project	NIA	NIA	University of Chicago
NCATS Pharmaceutical Collection	NCATS	NCATS	NCATS
NCBI BioSystems database	NLM	NLM	NLM
NCBI Bookshelf	NLM	NCBI Bookshelf	NLM
NCBI Epigenomics database	NLM	NLM	NLM
NCBI Gene database	NLM	NLM	NLM
NCBI Genome database	NLM	NLM	NLM
NCBI Nucleotide database	NLM	NLM	NLM
NCBI Protein database	NLM	NLM	NLM
NCBI Taxonomy Database	NLM	NLM	NLM
NEIBANK: EST Analysis and Bioinformatics for Ocular Genomics	NEI	NEI	NEI
Nephrotic Syndrome Study Network (NEPTUNE)	NIDDK	NIDDK	University of Michigan and DCC
Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC)	NIBIB	NIBIB, NCRR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIMH, NINDS, NINR, OBSSR	Turner Consulting Group, Inc.
NeuroQOL: quality-of-life outcomes instrument for CNS diseases	NINDS	NINDS	Northwestern University Feinberg School of Medicine
NHLBI Biologic Specimen & Data Repository	NHLBI	NHLBI	Precision Bioservices
NIA Genetics of Alzheimer's Disease Data Storage Site	NIA	NIA	University of Pennsylvania
NIA Primate Aging Database	NIA	NIA	University of Wisconsin, Madison
NIAID HIV-1, Human Protein Interaction Database	NIAID	NCBI, NIAID	DAIDS/NIAID and NCBI
NICEATM LLNA Database	NIEHS/NICEATM	NIEHS/NICEATM	NIEHS/NICEATM
NIDA Center for Genetic Studies	NIDA	NIDA	Rutgers University, with subcontract to Washington University at St. Louis
NIDCD National Temporal Bone, Hearing, and Balance Pathology Resource Registry	NIDCD	NIDCD	Massachusetts Eye and Ear Infirmary
NIDDK Central Repository: biosample repository	NIDDK	NIDDK	Fisher BioServices
NIDDK Central Repository: data repository	NIDDK	NIDDK	RTI International

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NIDDK Central Repository: genetics repository	NIDDK	NIDDK	Rutgers University
NIDDK Inflammatory Bowel Disease Genetics Consortium repository database	NIDDK	NIDDK	University of Chicago
NIDDK Information Network (dkNET)	NIDDK	NIDDK	University of California, San Diego
NIH AIDS Research and Reference Reagent Program	NIAID	NIAID	Fisher BioServices
NIH Blueprint for Neuroscience Research Neuroscience Information Framework	NIDA	NIBIB, NCCAM, NCRR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OD/OBSSR	University of California, San Diego
NIH Human Embryonic Stem Cell (hESC) Registry	OSP/OD	OSP/OD	OSP/OD
NIH NeuroBioBank	NIMH	NICHD, NIMH, NINDS	NIH, University of Miami Brain Endowment Bank; University of Maryland Brain and Tissue Bank; Harvard Brain Tissue Resource Center; Sepulveda Research Corporation; Mount Sinai Brain Bank; and University of Pittsburgh Brain Tissue Donation Program
NIH Pediatric MRI Data Repository Clinical Coordinating Center	NICHD	NIDA, NIMH, NICHD	Washington University
NIH Pediatric MRI Data Repository	NIMH	NIDA, NIMH, NICHD	McGill University and NIH
NIH Stem Cell Data Management System	NINDS	NINDS	NIH Stem Cell Unit and NINDS Division of Intramural Research
NIH Tetramer Core Facility	NIAID	NIAID	Emory/Yerkes
NIMH Chemical Synthesis and Drug Supply Program	NIMH	NIMH	RTI International
NIMH Human Brain Collection Core	NIMH	NIMH	NIMH
NIMH Repository and Genomics Resource	NIMH	NIMH	Washington University in St. Louis, Rutgers University, and University of Southern California
NINDS Common Data Elements	NINDS	NINDS	KAI Research, Inc.
NINDS Human Genetics Resource Center	NINDS	NINDS	Coriell Institute for Medical Research
NINDS/UC Davis NeuroMab Hybridoma Facility	NINDS	NINDS, NIMH, OD, NCATS	University of California, Davis
NLM Catalog	NLM	NLM	NLM

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Nonalcoholic Steatohepatitis Clinical Research Network's nonalcoholic fatty liver disease (NAFLD) database (adult and pediatric)	NIDDK	NIDDK	Johns Hopkins University and DCC
Nonhuman Primate HIV/SIV Vaccine Trials Database	NIAID	DoE, NIAID	Los Alamos National Laboratory
North American AIDS Cohorts Collaboration on Research and Design	NIAID	NIAID	Johns Hopkins University
Novel Markers of Prognosis in Hypertrophic Cardiomyopathy (HCMR)	NHLBI	NHLBI	University of Virginia
NTP historical control database	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
Nuclear Receptor Signaling Atlas	NIDDK	NIDDK	NIDDK
Observational Antiretroviral Studies in Southern Africa (OASIS) Collaboration	NIAID	NIAID	University of Berne, Switzerland
Online Mendelian Inheritance in Animals (OMIA)	NLM	NLM	NLM
Online Mendelian Inheritance in Man (OMIM)	NHGRI	NHGRI	Johns Hopkins University
OpenI image/text search system	NLM	NLM	NLM
OptiRNAi 2.0	NCI	NCI	NCI
Orthopedic image dataset	NLM	NLM	University of Southern California
Osteoarthritis Initiative (OAI) data coordination center	NIAMS	NIBIB, NIA, NIDCR, ORWH	University of California, San Francisco
PACEmaker & Beta-Blocker Therapy Post-Myocardial Infarct	NHLBI	NHLBI	Northwestern University at Chicago
Panel Study of Income Dynamics (PSID)	NIA	NIA	University of Michigan
Papillomavirus Episteme (PaVE)	NIAID	NIAID	NIAID
Parkinson's Disease Biomarkers Program database and repository	NINDS	NINDS	NINDS
PathoSystems Resource Integration Center (PATRIC)	NIAID	NIAID	University of Chicago
Pathway Commons: A Public Library of Biological Pathways	NHGRI	NHGRI	Sloan-Kettering Institute of Cancer Research
Pathway Interaction Database (PID)	NCI	NCI	NCI
Pediatric Acute Liver Failure Study Group	NIDDK	NIDDK	Pediatric Acute Liver Failure Study Group
Pediatric Cardiomyopathy Registry	NHLBI	NHLBI	University of Miami School of Medicine
Pediatric Imaging, Neurocognition, and Genetics (PING)	NIDA	NIDA	University of California, San Diego
Pharmacogenomics Knowledgebase (PharmGKB)	NIGMS	NIGMS, NLM	Stanford University
PhenoGen	NIAAA	NIAAA	University of Colorado, Denver
Pillbox	NLM	NLM	NLM

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Pleuropulmonary Blastoma DICER1 Syndrome Study	NCI	NCI	International Pleuropulmonary Blastoma Registry; International Ovarian and Testicular Stromal Tumor Registry; Children's Hospital, Washington, DC; and St. Louis Children's Hospital
PopSet	NLM	NLM	NLM
PorA VR3 Typing Database	NIAID	NIAID	NIAID
Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT)	NIDDK	NIDDK	Connecticut Children's Medical Center
Prevention of Renal Damage in Primary Hyperoxaluria	NIDDK	NIDDK	Mayo Clinic Rochester
Probe	NLM	NLM	NLM
Profiles in Science	NLM	NLM	NLM
Project MATCH database	NIAAA	NIAAA	University of Connecticut Health Center
Prostate Cancer Prevention Trial (PCPT) biorepository	NCI	NCI	Southwest Cooperative Oncology Group (SWOG)
Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO): Etiology and Early Marker Studies	NCI	NCI	NCI
Protein Clusters	NLM	NLM	NLM
Protein Data Bank		DoE, NIGMS, NLM, NSF, NCRR, NINDS, NCI, NIBIB	Rutgers, the State University of New Jersey; and University of California, San Diego
PubChem	NLM	CF	NLM
Public Use Data on Mexican Immigration	NICHD	NICHD	Princeton University
PubMed Central	NLM	NLM	NLM
PubMed/MEDLINE	NLM	NLM	NLM
qPrimerDepot	NCI	NCI	NCI
Quantification and Archiving of Pediatric MRI as an Educational Resource	NIBIB	NIBIB	Johns Hopkins University
Radiation Emergency Medical Management (REMM)	NLM	NLM	NLM
RAND Survey Meta Data Repository	NIA	NIA	University of Southern California
Rat Genome Database	NHLBI	NHLBI, NCI, NEI, NHGRI, NIA, NIAAA, NICHD, NIDCD, NIDDK, NIMH, NINDS	Medical College of Wisconsin
Reference Sequence Database (RefSeq)	NLM	NLM	NLM

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Registry and Surveillance System for Hemoglobinopathies	NHLBI	NHLBI	CDC
Repbase Update: a database of repetitive sequences	NLM	NLM	Genetic Information Research Institute
REpository for Molecular BRAin Neoplasia DaTa (REMBRANDT)	NCI, NINDS	NCI	NCI
Research Platform Integrating Patient Reported and Clinical Outcomes Data Sources	NLM	NLM	Dynamic Clinical Systems, Inc.
Research Resource for Complex Physiologic Signals	NIGMS	NIGMS, NIBIB	Beth Israel Deaconess Medical Center
Restoring Insulin Secretion (RISE)	NIDDK	NIDDK	George Washington University and DCC
Restriction Enzyme Database (REBASE)	NLM	NLM	New England Biolabs, Inc.
Retrovirus Epidemiology Donor Study III (REDS III)	NHLBI	NHLBI	RTI International
RxIMAGE: image dataset of prescription pills	NLM	NLM	NLM
RxNorm	NLM	NLM	NLM
Saccharomyces Genome Database	NHGRI	NHGRI	Stanford University
Salivary Gland Molecular Anatomy Project	NIDCR	NIDCR	NIDCR
Salivary Proteome Wiki	NIDCR, CIT	NIDCR, CIT	NIH
SpBase: sea urchin genome database	NICHD	NICHD	California Institute of Technology
SEARCH for Diabetes in Youth	NIDDK, CDC	NIDDK, CDC	Wake Forest School of Medicine and DCC
SEER-Medicare Linked Database	NCI	NCI	NCI
SEER-Medicare Health Outcomes Survey (MHOS) Linked Database	NCI	NCI	NCI
Selenium and Vitamin E Cancer Prevention Trial (SELECT) biorepository	NCI	NCI	Southwest Cooperative Oncology Group (SWOG)
Semantic LAMHDI: Linking Diseases to Model Organism Resources	OD/ORIP	OD/OIRP	Oregon Health and Science University
SenseLab: Integration of Multidisciplinary Sensory Data	NIDCD	NIDCD, NINDS	Yale University
Sequence Read Archive (SRA)	NLM	NLM	NLM
Severe Chronic Neutropenia International Registry	NIAID	NIAID	University of Washington
SHARE Israel	NIA	NIA	
Shared Database for the Study of Phonological Development	NICHD	NICHD	Carnegie-Mellon University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
Shared Database for the Study of Phonological Development	NICHD	NICHD	Carnegie-Mellon University
Short-term Outcomes of Interventions for Reproductive Dysfunction study patient registry	NICHD	NICHD	University of Oklahoma Health Sciences Center
Shwachman-Diamond Syndrome International Registry and Repository	NIAID	NIAID, NICHD	Fred Hutchinson Cancer Research Center
Single Nucleotide Polymorphism (SNP) Explorer	NIAID	NIAID	NIAID
Small Area Estimates of Cancer Risk Factors & Screening Behaviors	NCI	NCI	NCI
State Cancer Profiles	NCI	NCI, CDC	NCI
Statistical Methods for Integromics Discoveries	NLM	NLM	University of Pittsburgh
Surveillance, Epidemiology and End Results (SEER)	NCI	NCI	NCI
Survey of Health, Ageing, and Retirement in Europe	NIA	NIA	Munich Center for the Economics of Aging
Swedish Adoption/Twin Study of Aging (SATSA)	NIA	NIA	Karolinska Institutet
Systematic Data Curation and Integration to Link Models of Human Disease	OD/ORIP	OD/ORIP	Princeton University
Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS)	NIDDK	NIDDK	Cincinnati Children's Hospital Medical Center and DCC
The Cancer Imaging Archive	NCI	NCI	NCI
The Environmental Determinants of Diabetes in the Young (TEDDY)	NIDDK	NIDDK	University of South Florida and DCC
Tobacco Use Supplement to the Current Population Survey	NCI	NCI	U.S. Census Bureau
ToxFX	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
Toxics Release Inventory (TRI)	NLM	NLM	EPA
TOXLINE: toxicology literature online	NLM	NLM	NLM
TOXMAP: Environmental Health Maps	NLM	NLM	EPA
Trace Assembly Archive	NLM	NLM	NLM
Transcriptome Resources	NIAID	NIAID	NIAID
Transporter Classification Database (TCDB)	NIGMS	NIGMS, NIAID, NLM	University of California, San Diego
Trauma-related database	NIGMS	NIGMS	Massachusetts General Hospital
Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, follow-up, and genetics study	NIDDK	NIDDK	George Washington University and DCC
Turning The Pages: rare historic works	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institution(s)
Type 1 Diabetes TrialNet	NIDDK	NIDDK	University of South Florida and DCC
Type 2 Diabetes Genetic Consortium (T2DGC) [now part of the Foundation for NIH's Accerelating Medicines Partnership]	NIDDK	NIDDK	Multiple
Unified Medical Language System (UMLS)	NLM	NLM	NLM
Unified Medical Language System (UMLS)-based Archive System for Digital Resources	NLM	NLM	Johns Hopkins University
UniGene	NLM	NLM	NLM
UniProt Knowledgebase	NHGRI	NHGRI, NIGMS,	European Molecular Biology Laboratory
United States Immunodeficiency Network (USIDNET)	NIAID	NIAID	Immune Deficiency Foundation
United States Renal Data System (USRDS)	NIDDK	NIDDK	NIDDK
University of Maryland Brain and Tissue Bank	NICHD	NICHD	University of Maryland
University of Washington Center for Mendelian Genomics	NHGRI	NHGRI, NHLBI	University of Washington
Using Medical Informatics Principles to Enhance Development and Dissemination of Clinical Practice Guidelines on Major Depressive Disorder	NLM	NLM	American Psychiatric Foundation
VectorBase: invertebrate vectors of human pathogens	NIAID	NIAID	University of Notre Dame
Vietnam Era Twin Study of Aging	NIA	NIA	Boston University
Virus Pathogen Database and Analysis Resource (ViPR)	NIAID	NIAID	Northrup Grummon Health IT and J. Craig Venter Institute
Wireless Information System for Emergency Responders (WISER)	NLM	NLM	NLM
Wisconsin Longitudinal Study	NIA	NIA	University of Wisconsin
Wisconsin Registry for Alzheimer Prevention: biomarkers of preclinical AD	NIA	NIA	University of Wisconsin, Madison
World Health Organization (WHO) Study on Global Ageing and Adult Health	NIA	NIA	World Health Organization
Xenbase: A Xenopus Model Organism Database	NICHD	NICHD	Cincinnati Children's Hospital Medical Center
XNAT open-source informatics for imaging research	NIBIB	NIBIB	Washington University
ZFIN: The Zebrafish Model Organism Database	NHGRI	NHGRI	University of Oregon

Appendix H: Actions Undertaken to Carry Out Scientific Frameworks on Recalcitrant Cancer

In response to the Recalcitrant Cancer Research Act of 2012 (see Appendix A for details), NCI recently developed scientific frameworks for two recalcitrant cancers:

- *Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)*[790]
- *Scientific Framework for Small Cell Lung Cancer (SCLC)*[791]

This appendix includes an assessment of the progress made in improving outcomes for individuals diagnosed with these cancers; an update on activities pertaining to these cancers, including actions undertaken to carry out the two scientific frameworks; and information on research grants awarded by NIH for research relating to these cancers.

Assessment of Progress

In the U.S., PDAC is the fourth leading cause of cancer-related death in both men and women, and it has a five-year relative survival rate of less than 5 percent. In part because pancreatic cancer is usually diagnosed at an advanced stage, the survival rate is extremely low compared with rates for many other cancer types. Between 2001 and 2010, the incidence of pancreatic cancer incidence increased by more than 10 percent, while the mortality rate increased by almost 5 percent.

SCLC has a similarly low five-year relative survival rate, less than 7 percent. As noted in the Scientific Framework on SCLC, the disease is highly associated with cigarette smoking, and the decrease in cigarette smoking in the U.S. population is reflected in the decrease in the incidence of SCLC over the past 30 years, with continued decreases expected.

Although the framework for the biennial reports indicates a request for relative survival rates, NCI prefers to use mortality rates. Relative survival rates may be misleading for at least two reasons. First, there may be lead-time bias, where diagnosis earlier in the disease but without an improved clinical response is recorded incorrectly as improvement. Second, relative survival rates focus only on those patients who develop the disease. This is an important consideration for SCLC, where tobacco consumption is an important risk factor, and probably to some degree for PDAC. For example, if decreased smoking led to a 50 percent reduction in the incidence and mortality of SCLC, then that change would be seen as progress, even if there were no change in relative survival rate. Mortality rates do not have these shortcomings.

NCI calculates mortality rates using population-level data collected through its Surveillance, Epidemiology, and End Results program. When looking to assess progress made in improving these rates, the time necessary to collect and analyze the data is a critical factor. One problem inherent in estimating mortality rates is that patient cohorts must be followed for a number of years after diagnosis in order to calculate accurate rates. Data that will be used to calculate relative mortality rates for patients diagnosed with PDAC and SCLC in recent years are still being collected.

As described in detail in the *Scientific Framework for PDAC*[784] and the *Scientific Framework for SCLC*,[785] NCI is supporting critical research that aims to improve outcomes in each of these disease areas. Scientific progress is being made to better understand both PDAC and SCLC, and NCI continues to prioritize research in these areas in an effort to translate this progress to improved prevention, diagnosis, treatment, and quality of life for patients.

[790] For more information, see http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf.
[791] For more information, see http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLC%20Congressional%20Response.pdf.

Update on PDAC and SCLC Activities (2012-2013)

NCI's research framework for PDAC was examined during a multidisciplinary workshop convened in late 2011 to develop additional forward-looking scientific approaches for this recalcitrant disease. The workshop report, *Pancreas Cancer: Scanning the Horizon for Focused Interventions*,[792] was developed over the following year and was presented to and accepted by the NCI Clinical Trials and Translational Research Advisory Committee in March 2013.

One of the framework recommendations was for NCI and NIDDK to collaborate to explore the connections between diabetes and pancreatic cancer. In June 2013, NIDDK and NCI, together with the Pancreatic Cancer Action Network, sponsored a two-day interdisciplinary meeting, the NIDDK-NCI Pancreatitis-Diabetes-Pancreatic Cancer Workshop,[793] as an initial step toward understanding the clinical and biological relationships between chronic pancreatitis, PDAC, and diabetes. The purpose of the workshop was to explore the known and suspected mechanisms for the increased risk for PDAC associated with chronic pancreatitis and diabetes, identify the prevalence of type 3c diabetes (diabetes associated with diseases of the pancreas) in the overall diabetes population, assess strategies to differentiate type 3c diabetes from type 2 diabetes, review the effects of anti-diabetic therapy on the development of PDAC, and explore possible PDAC surveillance methods for patients with type 2 and 3c diabetes. Participants defined high-priority strategies that need to be pursued in the areas of mechanisms, biomarkers, and refinement of risk. Efforts are currently underway to move forward a collaborative agenda for expanding research in all areas considered critical.

In late 2013, the Center of Excellence in Immunology at NCI's intramural Center for Cancer Research sponsored a two-day conference, Inflammation, Microbiota, and Cancer. This conference discussed many aspects of cell–cell and cell–mediator interactions that are important to immunotherapy of pancreatic cancer. Potentially important new approaches were identified and are informing research plans.

Many common cancers are driven by mutant forms of the RAS proteins. Mutations in KRAS have been implicated in 95 percent of PDAC cases, 45 percent of colorectal cancers, and 35 percent of lung adenocarcinomas. Although there have been many attempts at targeting cancer cells driven by KRAS, successful strategies have so far been elusive. Recent discoveries provide opportunities to make progress on this front. In early 2013, NCI held a series of meetings with experts in the RAS field to discuss appropriate projects to pursue; NCI has mounted a large-scale program on RAS, and five projects were defined as having high priority:

- The first two projects involve structural and biological approaches to attack RAS directly.
- The third project, disrupting KRAS complexes within cells, presents new opportunities for drug discovery.
- The fourth project will define the landscape of proteins on the surface membranes of cells that have mutations in KRAS and will facilitate the development of direct antibody-mediated interventions, immune-based therapies—such as adoptive transfer of T cells engineered to attack tumor antigens—and nanoparticle-mediated drug delivery.
- The fifth project will conduct synthetic lethality screens, including those in three-dimensional cell cultures and animals, to discover combinations of proteins that cells with mutant KRAS require for survival. Results from this project could lead to the development of new combinations of targeted therapies.

These five projects, which were unanimously approved by the NCI Board of Scientific Advisors and the National Cancer Advisory Board at their joint meeting in June 2013, have been initiated within a "RAS community," by a hub-and-spoke model: Scientific leaders, core facilities, and critical technologies and materials are being provided by the Advanced Technologies Research Facility at the FNLCR "hub," and a community of investigators at academic institutions, pharmaceutical and biotechnical companies, and the NCI intramural research program are serving as the "spokes."

In addition to these initiatives, NCI also has three Pancreatic Cancer Epidemiology Consortia and two pancreatic cancer–specific Specialized Programs of Research Excellence (SPOREs) that are building knowledge and capacity in this specialty.

[792] For more information, see http://deainfo.nci.nih.gov/advisory/ctac/workgroup/ctacsupmat.htm.
[793] For more information, see http://www2.niddk.nih.gov/News/Calendar/PDPC2013.htm.

FY 2013 NCI Grants Related to PDAC

Project Number	Investigator	Project Title	Institution
1F30CA177123-01	Ferreira, Mark	Transcriptional Coregulation in Pancreatic Adenocarcinoma Progression	University of Pennsylvania
1F30CA180601-01	Bakir, Basil	The Role of p120ctn in Pancreatic Ductal Morphogenesis and Adenocarcinoma	University of Pennsylvania
1F31CA177153-01	Streicher, Samantha	Genome-wide Case-control Association Study of Pancreatic Cancer in Jews	Yale University
1F31CA180392-01	Kendrick, Agnieszka	The activity and molecular interactions of extracellular EMMPRIN	University of Colorado
1F31CA180682-01	Makohon-Moore, Alvin	Subclonal Evolution in Metastatic Pancreatic Cancer	Johns Hopkins University
1F31CA180693-01	Hayes, Tikvah	Targeting K-Ras effector signaling for pancreatic cancer treatment	University of North Carolina at Chapel Hill
1F31CA180738-01	Badgley, Michael	Genetic and pharmacological manipulation of system xc in pancreatic cancer	Columbia University Health Sciences
1F32CA177072-01	Livshits, Geulah	Mechanisms of tumor suppression by epigenetic regulators in pancreatic cancer	Sloan-Kettering Institute for Cancer Research
1F32CA180374-01	Fujimura, Ken	Deciphering the Role of eIF5A/PEAK1 Pathway in Pancreatic Cancer	University of California, San Diego
1F32CA180606-01	Staley, Binnaz	Investigating YAP's role during pathogenesis of pancreatic ductal adenocarcinoma	University of California, San Francisco
1K08CA172676-01A1	Carpizo, Darren	Exploration of a Mutant p53 Reactivating Compound	Rutgers Biomedical and Health Sciences Cancer Institute of New Jersey
1K25CA164248-01A1	Kanick, Stephen	Quantitative optical dosimetry of magnetic nanoparticle cancer treatments	Dartmouth College
1K25CA166178-01A1	Gong, Shaoqin	Targeted Therapy of Neuroendocrine Cancers via the Notch Signaling Pathway	University of Wisconsin-Madison
1R01CA166150-01A1	Michaud, Dominique	Microbiomes in Human Pancreatic Cancer	Brown University
1R01CA167291-01A1	Kelley, Mark	Novel Role of Ref-1 in Pancreatic Cancer Etiology and Progression	Indiana University–Purdue University Indianapolis
1R01CA167535-01A1	Kester, Mark	Novel Nanoparticle Therapy for Pancreatic Cancer	Pennsylvania State University

Project Number	Investigator	Project Title	Institution
1R01CA168448-01A1	Yamamoto, Masato	Next Generation Oncolytic Adenovirus for Advanced Pancreatic Cancer Treatment	University of Minnesota
1R01CA168611-01A1	Miller, George	Toll-like Receptor Regulation of Pancreatic Tumorigenesis	New York University School of Medicine
1R01CA168863-01A1	Linehan, David	CCR2 Blockade in Human Pancreatic Cancer	Washington University
1R01CA169046-01A1	Buettner, Garry	The chemical biology of pharmacological ascorbate in cancer treatment	University of Iowa
1R01CA169086-01A1	Thayer, Sarah	PDG Links Stem Cell Niche to Pancreatic Epithelial Renewal, Repair, and Cancer	Massachusetts General Hospital
1R01CA169122-01A1	Wei, Peng	Genetic Susceptibility and Risk Model for Pancreatic Cancer	University of Texas Health Science Center Houston
1R01CA169281-01A1	Han, Haiyong	Targeting Stromal Collagen in Pancreatic Cancer	Translational Genomics Research Institute
1R01CA169702-01A1	Zheng, Lei	Annexin A2 as a mediator of pancreatic cancer metastases	Johns Hopkins University
1R01CA172233-01A1	Xie, Keping	Molecular Mediators of Pancreatic Cancer Invasion and Progression	University of Texas MD Anderson Cancer Center
1R01CA172380-01	Meeker, Alan	Determining the Roles of ATRX and DAXX Abnormalities in Cancer Telomere Biology	Johns Hopkins University
1R01CA172431-01A1	Yang, Guang-Yu	Inhibition of pancreatic carcinogenesis via targeting c-Raf and sEH	Northwestern University
1R01CA172880-01A1	Jiao, Li	Advanced Glycation End-Products and Risk of Pancreatic Cancer	Baylor College of Medicine
1R01CA176828-01A1	Goggins, Michael	Using Markers to Improve Pancreatic Cancer Screening	Johns Hopkins University
1R01CA177857-01	Davis, Brian	Role of Neurogenic Inflammation in Pancreatic Cancer	University of Pittsburgh
1R01CA179991-01	Iacobuzio-Donahue, Christine	(PQB6) Genetics of Subclonal Evolution in Pancreatic Cancer	Johns Hopkins University
1R01CA180057-01	Guttridge, Denis	(PQD6) Muscle stem cells and cancer cachexia	Ohio State University
1R03CA166664-01A1	Rogers, Connie	Role of Obesity-Induced Immunosuppression in Pancreatic Cancer	Pennsylvania State University–University Park
1R03CA166910-01A1	Mukherjee, Pinku	MUC1 regulation of TGF-beta function in pancreatic cancer cells	University of North Carolina at Charlotte
1R03CA166912-01A1	Shah, Kavita	Chemical Genetic Dissection of Aurora A in Promoting EMT and Stem Cells Phenotype	Purdue University
1R03CA169692-01A1	Du, Yuchun	Identification of the molecules/ pathways that confer acquired radioresistance in	University of Arkansas

Project Number	Investigator	Project Title	Institution
1R03CA173223-01	Solheim, Joyce	Flt3L Treatment of Pancreatic Cancer	University of Nebraska Medical Center
1R03CA173273-01	Yang, Wensha	Improving Pancreas RT Plans using Respiration-driven Anatomic Deformation	Cedars-Sinai Medical Center
1R15CA173668-01	Mukherjee, Pinku	MUC1 enhances Neuropilin-1 signaling in pancreatic ductal adenocarcinoma	University of North Carolina at Charlotte
1R21CA164245-01A1	Faller, Douglas	Non-Oncogene Addiction as a Targeted Therapy for Pancreatic Cancer	Boston University Medical Campus
1R21CA164756-01A1	Ferrone, Soldano	Grp94 targeted therapy for pancreatic ductal adenocarcinoma	Massachusetts General Hospital
1R21CA167329-01A1	North, William	NMDA receptors in the diagnosis and treatment of pancreatic cancer	Dartmouth College
1R21CA169611-01A1	Taylor, Derek	Targeting Telomerase in Pancreatic Cancer	Case Western Reserve University
1R21CA169706-01A1	Yen, Timothy	Chemosensitization of Pancreatic Cancer Cells by Curcumin and Vitamin D Receptor	Research Institute of Fox Chase Cancer Center
1R21CA169717-01A1	Gross, Kenneth	Epi)Genomic drivers of primary and metastatic pancreatic islet cell carcinoma	Roswell Park Cancer Institute
1R21CA169720-01A1	Zhou, Tong	Novel Anti-HER3 Strategy for Pancreatic Cancer	University of Alabama at Birmingham
1R21CA169741-01A1	Puré, Ellen	The role of the stromal cell surface protease FAP in pancreatic cancer	Wistar Institute
1R21CA169757-01A1	Quy Hoa Le Thi, Anne	Profiling Pancreatic Cancer Metabolism and Tumor Microenvironment for Therapy	Johns Hopkins University
1R21CA169844-01A1	Cuevas, Carlos	Minimally invasive ablative therapies for pancreatic cystic neoplasms	University of Washington
1R21CA169849-01A1	Dowdy, Steven	Novel Cell Cycle Therapeutic Targets in Pancreatic Cancer	University of California, San Diego
1R21CA170041-01A1	Hayman, Michael	HDAC3 - a therapeutic target in PDA	State University of New York at Stony Brook
1R21CA170121-01A1	Matters, Gail	Targeting Pancreatic Cancer with Aptamers to the CCK-B Receptor	Pennsylvania State University
1R21CA170995-01A1	Sun, Yi	Anti-pancreatic tumorigenesis by inactivation of SAG/RBX2 E3 ubiquitin ligase	University of Michigan
1R21CA172983-01A1	Stan, Radu	Anti-PV1 Therapy for Pancreatic Cancer	Dartmouth College
1R21CA172997-01A1	Azad, Nilofer	Targeting RAS signaling with CDK and AKT inhibition in pancreatic cancer	Johns Hopkins University
1R21CA173297-01A1	Cohn, Susan	Mechanisms of Pancreatic Cancer Inhibition by SPARC	University of Chicago

Project Number	Investigator	Project Title	Institution
1R21CA173348-01A1	Du, Yi-Chieh Nancy	Autophagy in Pancreatic Neuroendocrine Tumor Growth and Metastasis	Weill Medical College of Cornell University
1R21CA173473-01	Phelps, Mitch	Optimizing selective in vivo inhibition of pancreatic tumor JAK2/STAT3 signaling	Ohio State University
1R21CA173487-01	Brekken, Rolf	Axl as a target for the therapy of pancreatic cancer	University of Texas Southwestern Medical Center
1R21CA173518-01A1	Boucher, Yves	Breakdown of Desmoplasia in Pancreatic Cancer to Enhance Drug Effectiveness	Massachusetts General Hospital
1R21CA173605-01A1	Winter, Jordan	MUC1-Targeted Nanotherapy for Pancreatic Cancer	Thomas Jefferson University
1R21CA174306-01A1	Diamond, Don	IDO-silencing Salmonella therapy for the treatment of primary and metastatic PDAC	City of Hope/Beckman Research Institute
1R21CA174594-01A1	Celedon, Alfredo	Single molecule microarrays for the detection of mutant DNA in body fluids	Twistnostics, LLC
1R21CA175974-01	Mohammad, Ramzi	Differential Network Interrogations of Epithelial to Mesenchymal Transition	Wayne State University
1R21CA176222-01	Guzman, Esther	Targeting RAGE in pancreatic cancer	Florida Atlantic University
1R21CA176267-01	Krishna, Nepalli	C-Src Kinase-Calmodulin Interaction: A Therapeutic Target For Pancreatic Cancer	University of Alabama at Birmingham
1R21CA176337-01	Pietras, Richard	Development of New Therapeutics for Pancreatic Cancer Management	University of California, Los Angeles
1R21CA176339-01	Li, Shyh-Dar	Stromal depletion for pancreatic cancer therapy	Ontario Institute for Cancer Research
1R21CA176535-01	Harding, Joseph	Evaluation of MSP Antagonists for the Treatment of Pancreatic Cancer	Washington State University
1R21CA178651-01	Jackson, Mark	A RAS-FAM83A Regulatory Loop as a Novel Therapeutic Target for Pancreatic Cancer	Case Western Reserve University
1R21CA179379-01	Zhang, Xiao-Kun	Role of tRXRalpha in pancreatic cancer development and therapy	Sanford-Burnham Medical Research Institute
1R21CA179453-01	Murtaugh, Lewis	An epigenetic switch controlling pancreatic cancer susceptibility	University of Utah
1R21CA179489-01	Saez, Enrique	Targeting Adipocyte Lipases to Treat Pancreatic Cancer-Associated Cachexia	Scripps Research Institute
1R21CA182608-01	Cheng, Ji-Xin	Quantitative Spectroscopic Imaging of Cancer Metabolites in Live Cells and Intact	Purdue University
1R43CA167964-01A1	Zinnen, Shawn	Novel Vitamin B6 based prodrugs of gemcitabine	MCB Research, Inc.

Project Number	Investigator	Project Title	Institution
1R43CA171744-01A1	Wegener, William	Localization of Pancreatic Cancer by a Pretargeted 18F-Hapten-Peptide	Immunomedics, Inc.
1R43CA174025-01A1	Pantazis, Panayotis	Development of Monoclonal Antibodies To Treat Pancreatic Cancer	COARE Biotechnology, Inc.
1R43CA176942-01	Monahan, Joseph	Development of TAK1 Inhibitors to Treat Pancreatic Cancer	Confluence Life Sciences LLC
1R43CA176957-01	Hyland, Kendra	Sleeping Beauty Mediated Therapy for Alpha V Beta 6-Expressing Pancreatic Cancer	Discovery Genomics, Inc.
1R43CA180398-01	Chan, Kyle	Pre-clinical development of a novel pancreatic cancer chemotherapeutic	Biotheryx, Inc.
2R01CA033084-30A1	Greenberg, Philip	Mechanisms of Murine Tumor Eradication by Immunotherapy	University of Washington
2R01CA054358-20A1	Feinberg, Andrew	Epigenetic Drivers of Cancer Progression	Johns Hopkins University
2R01CA097022-11	Klemke, Richard	Survival Mechanisms of Invasive Carcinoma Cells	University of California, San Diego
2R01CA097061-10A1	Stockwell, Brent	Chemical genetic profiling of engineered tumor cells	Columbia University
2R01CA122589-06A1	Ellisen, Leif	Function and mechanism of REDD1/ mTOR signaling in metabolism and tumorigenesis	Massachusetts General Hospital
2R01CA124586-06A1	Konieczny, Stephen	Kras-Induced Cellular Plasticity in Pancreatic Cancer	Purdue University
2R01CA124723-06	Saluja, Ashok	The Inhibition of HSP70 Induces Apoptosis in Pancreatic Cancer Cells	University of Minnesota
2R01CA135274-06A1	Cui, Zhengrong	Overcoming pancreatic tumor resistance to gemcitabine	University of Texas, Austin
3P50CA102701-10S1	Petersen, Gloria	Mayo Clinic SPORE in Pancreatic Cancer	Mayo Clinic Rochester
3R01CA105412-10S1	Quigley, James	Transmembrane Proteins Involved in Human Tumor Expansion	Scripps Research Institute
3R01CA126888-05S1	Munshi, Hidayatullah	Fibrosis-Protease Cross-Talk Regulating Pancreatic Cancer Invasion	Northwestern University
3R01CA136754-05S1	Lin, Richard	Phosphatidylinositol 3-kinase and prevention of pancreatic cancer	State University of New York at Stony Brook
3R01CA136786-05S1	Blobe, Gerard	Function of TbRIII as a BMP Co-receptor in Human Cancer	Duke University
3R01CA153821-04S1	Hurley, Laurence	G-Quadruplex-Mediated Transcriptional Regulation of PDGFR-β	University of Arizona
3R01CA154846-03S1	Mao, Hui	MRI Capable Receptor Targeted Drug Delivery for Pancreatic Cancer	Emory University
3R21CA169717-01A1S1	Gross, Kenneth	Epi)Genomic drivers of primary and metastatic pancreatic islet cell carcinoma	Roswell Park Cancer Institute

Project Number	Investigator	Project Title	Institution
3R41CA159657-01A1S1	Gurova, Katerina	Testing of novel anti-cancer compounds Curaxins against pancreatic cancer	Buffalo Biolabs, LLC
4R00CA155045-04	Celli, Jonathan	Mechanism-based therapies for pancreatic cancer informed by stromal microrheology	University of Massachusetts Boston
5F30CA167963-02	Carpenter, Eileen	Defining PI3K p110alpha as a therapeutic target in pancreatic cancer	State University of New York at Stony Brook
5F30CA168063-02	Quattrochi, Brian	Roles of MiR-17-92 Cluster MicroRNAs in K-Ras-Induced Pancreatic Tumorigenesis	University of Massachusetts Medical School
5F31CA165603-02	Fako, Valerie	Molecular Mechanism of Orlistat Hydrolysis by FASN for Targeted Drug Discovery	Indiana University–Purdue University Indianapolis
5F31CA165623-02	Stratford, Jeran	Role of TTK/Mps-1 upregulation by Ral GTPase activation in pancreatic oncogenesis	University of North Carolina at Chapel Hill
5F31CA168117-02	Butler, Amanda	PKCz; a novel therapeutic target for pancreatic cancer 'stem cells'	Mayo Clinic Jacksonville
5F32CA144579-03	Whipple, Chery	The Role of glypican-1 in Pancreatic Cancer Development and Progression	Dartmouth College
5F32CA165785-02	Bekes, Erin	Non-Cell Autonomous Functions of N-cadherin in KRas-driven Preneoplastic Lesions	New York University School of Medicine
5K07CA140790-05	Wolpin, Brian	Cohort Study of Biochemical and Genetic Risk Factors for Pancreatic Cancer	Dana-Farber Cancer Institute
5K08CA137153-04	Collisson, Eric	A Model for Preclinical Biomarker Discovery in Pancreatic Ductal Adenocarcinoma	University of California, San Francisco
5K08CA138907-03	Beatty, Gregory	CD40 Pathway in Pancreatic Adenocarcinoma	University of Pennsylvania
5K08CA138912-05	Hwang, Rosa	Stromal Periostin in Pancreatitis and Pancreas Cancer	MD Anderson Cancer Center
5K08CA142903-03	White, Rebekah	RNA Therapeutics for Pancreatic Cancer	Duke University
5K08CA142904-04	Camp, Ernest	Innovative Delivery Strategy for CaSm Gene Therapy in Pancreatic Cancer	Medical University of South Carolina
5K23CA148964-04	Zheng, Lei	Dissecting the mechanisms of immune tolerance within the pancreatic tumor's microenvirnoment	Johns Hopkins University
5K23CA163672-02	Le, Dung	Cyclophosphamide modified GM-CSF pancreatic tumor vaccine + listeria-mesothelin	Johns Hopkins University
5K25CA137222-04	Pan, Sheng	Quantitative glycoproteomics for pancreatic cancer studies	University of Washington

Project Number	Investigator	Project Title	Institution
5P01CA117969-08	Depinho, Ronald	Genetics and Biology of Pancreatic Ductal Adenocarcinoma	MD Anderson Cancer Center
5P01CA134292-05	Leach, Steven	Functional Annotation of the Pancreatic Cancer Genome	Johns Hopkins University
5P01CA163200-02	Eibl, Guido	Targeting diet-induced promotion of Kras-initiated pancreatic adenocarcinoma	University of California, Los Angeles
5P50CA101955-09	Buchsbaum, Donald	UAB / UMN SPORE in Pancreatic Cancer	University of Alabama at Birmingham
5R00CA139050-05	McNally, Lacey	KiSS1 treatment of pancreatic adenocarcinoma	University of Louisville Research Foundation
5R01CA042829-19	Schuller, Hildegard	GABA-B-R-mediated prevention of pancreatic cancer	University of Tennessee
5R01CA042978-27	Der, Channing	Biological Activity of Ras Oncogenes	University of North Carolina at Chapel Hill
5R01CA055360-22	Bar-Sagi, Dafna	Mechanisms of Signal Transduction by Ras Proteins	New York University School of Medicine
5R01CA069122-14	Freeman, James	Role of TGFBeta alterations in pancreatic cancer	University of Texas Health Science Center at San Antonio
5R01CA094084-10	Yamamoto, Masato	Enhanced CRAd for Pancreatic Cancer	University of Minnesota
5R01CA096924-08	Gold, David	Detection and Diagnosis of Pancreatic Carcinoma	Center for Molecular Medicine/Immunology
5R01CA097159-09	Chiao, Paul	Mechanisms of RelA Activation in Cancer	MD Anderson Cancer Center
5R01CA104125-09	McNiven, Mark	Cytoskeletal Dynamics in Pancreatic Cancer Metastasis	Mayo Clinic Rochester
5R01CA105412-10	Quigley, James	Transmembrane Proteins Involved in Human Tumor Expansion	Scripps Research Institute
5R01CA109525-09	Su, Gloria	Mouse Model for Human Pancreatic Ductal Adenocarcinoma	Columbia University Health Sciences
5R01CA112537-09	Hebrok, Matthias	Embryonic signaling pathways in pancreatic cancer	University of California, San Francisco
5R01CA113669-09	Maitra, Anirban	Developmental Signaling Pathways in Pancreatic Cancer	Johns Hopkins University
5R01CA127494-05	McConkey, David	Proteasome Inhibition and ER Stress	MD Anderson Cancer Center
5R01CA129038-05	Srivastava, Sanjay	Chemoprevention of Pancreatic Cancer by Capsaicin	Texas Tech University Health Sciences Center
5R01CA129357-05	Hingorani, Sunil	Genetic progression of pancreatic mucinous cystic neoplasms to invasive carcinoma	Fred Hutchinson Cancer Research Center
5R01CA129967-05	Mitchell, Robert	Amplification of tumor hypoxic responses by MIF-dependent HIF stabilization	University of Louisville Research Foundation

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5R01CA132794-05	Sarkar, Fazlul	FoxM1: A molecular target in pancreatic cancer	Wayne State University
5R01CA132971-05	Bouvet, Michael	Color-Coded Imaging of Pancreatic Cancer Microenvironment for Drug Discovery	University of California, San Diego
5R01CA133557-06	Bardeesy, Nabeel	TGF-beta Signaling in Pancreatic Cancer	Massachusetts General Hospital
5R01CA135011-05	Mukherjee, Priyabrata	Development of a gold nanoparticles based targeted delivery system	Mayo Clinic Rochester
5R01CA136526-05	Fernandez-Zapico, Martin	Hedgehog and EGF interaction: a novel therapeutic approach for pancreatic cancer	Mayo Clinic Rochester
5R01CA136754-05	Lin, Richard	Phosphatidylinositol 3-kinase and prevention of pancreatic cancer	State University of New York at Stony Brook
5R01CA136786-05	Blobe, Gerard	Function of TbRIII as a BMP Co-receptor in Human Cancer	Duke University
5R01CA138461-05	Wang, Liewei	Pharmacogenomics and Mechanisms of Cytidine Analogues	Mayo Clinic Rochester
5R01CA138701-04	Li, Min	Role of Dietary Zinc Transporter ZIP4 in Pancreatic Cancer	University of Texas Health Science Center at Houston
5R01CA138723-04	Maybaum, Jonathan	Mechanism-Based Use of Chk1 Inhibitors in Pancreas Cancer	University of Michigan
5R01CA140182-04	Storz, Peter	Protein Kinase D in oncogenic oxidative stress signaling	Mayo Clinic Jacksonville
5R01CA140211-05	Misek, David	Distinctive Glycan Fingerprints of Pancreatic Cancer for Plasma Detection	University of Michigan
5R01CA140290-03	Murray, Nicole	Role of PKC iota in metaplasia and initiation of pancreatic cancer	Mayo Clinic Jacksonville
5R01CA140410-04	Chiao, Paul	Function and Regulation Mechanisms of Polo-like Kinase 3 in Pancreatic Cancer	MD Anderson Cancer Center
5R01CA140424-04	Yeh, Jen Jen	Targeting Ras-Ral GEF-Ral Effector Signaling for Pancreatic Cancer Treatment	University of North Carolina at Chapel Hill
5R01CA140550-04	Tang, Amy	SIAH2-Dependent Proteolysis in Cell Migration, Tumor Growth and Cancer Metastasis	Eastern Virginia Medical School
5R01CA140582-04	Zhang, Jian-Ting	Therapeutic targeting of stratifin structure and function	Indiana University–Purdue University Indianapolis
5R01CA140599-05	Iacobuzio-Donahue, Christine	TGF-beta Signaling in Pancreatic Cancer Progression	Johns Hopkins University
5R01CA140875-03	Attardi, Laura	Mouse Models to Dissect p53 Tumor Suppressor Function	Stanford University
5R01CA140940-04	Sherman, Simon	Enhancing the Biomedical Computing Platform for Pancreatic Cancer Research	University of Nebraska Medical Center

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5R01CA142674-04	Chiao, Paul	Mechanisms of Overexpressed TrkB in Inducing Pancreatic Cancer Metastasis	MD Anderson Cancer Center
5R01CA142736-04	Chauhan, Subhash	Aspects of MUC13 Mucin in Cancer	Sanford Research/ University of South Dakota
5R01CA148954-04	Xie, Keping	Genetic Approaches to Pancreatic Cancer Progression	MD Anderson Cancer Center
5R01CA150142-03	Matsui, William	Cellular diversity and clinical relevance of stem cells in pancreatic cancer	Johns Hopkins University
5R01CA150190-04	Mukhopadhyay, Debabrata	Targeting Pancreatic Cancer Using Peptide Chemistry: From Bench to Bedside	Mayo Clinic Rochester
5R01CA151588-04	Pasca Di Magliano, Marina	Gli Activity in the Pancreas: Inflammation, Tissue Repair and Cancer	University of Michigan
5R01CA151727-03	Dhar, Animesh	Pancreatic Cancer: Crocetin as a Novel Therapeutic Approach	University of Kansas Medical Center
5R01CA152309-04	Xie, Keping	Functional Validation of Pancreatic Cancer Progression Biomarker	MD Anderson Cancer Center
5R01CA153821-04	Hurley, Laurence	G-Quadruplex-Mediated Transcriptional Regulation of PDGFR-β	University of Arizona
5R01CA154172-04	Rigas, Basil	Phospho-valproic acid for pancreatic cancer prevention	State University of New York at Stony Brook
5R01CA154321-03	Sarkar, Fazlul	Prevention of Tumor Progression by a Novel Approach	Wayne State University
5R01CA154383-03	Bergers, Gabriele	Multipotential mesenchymal stem cell-like cells in pancreatic tumorigenesis	University of California, San Francisco
5R01CA154451-03	Hwang, Joo	Ultrasound enhanced penetration for treatment of pancreatic cancer	University of Washington
5R01CA154455-03	Lubman, David	Serum glycoprotein markers of cancer using an ion mobility/mass spec approach	University of Michigan
5R01CA154517-03	Petersen, Gloria	Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment	Mayo Clinic Rochester
5R01CA154823-03	Klein, Alison	Validation and Fine-Scale Mapping of Pancreatic Cancer Susceptibility Loci	Johns Hopkins University
5R01CA154846-03	Mao, Hui	MRI Capable Receptor Targeted Drug Delivery for Pancreatic Cancer	Emory University
5R01CA155198-02	Leopold, Judith	Design of MEK Inhibitor Regimens for the Treatment of Pancreatic Cancer	University of Michigan
5R01CA155620-03	Lowy, Andrew	RON Receptor in Pancreatic Cancer Biology and Therapy	University of California, San Diego

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5R01CA155784-03	Lewis, Brian	Dissecting Hedgehog, TGF beta and BMP Signaling During Pancreatic Tumorigenesis	University of Massachusetts Medical School
5R01CA157490-03	Kimmelman, Alec	Investigating the Role of Autophagy in Pancreatic Cancer Radiation Resistance	Dana-Farber Cancer Institute
5R01CA157738-02	Liu, Rihe	Novel Single Domain Antibodies with Multivalency and Multispecificity	University of North Carolina at Chapel Hill
5R01CA157980-03	Olive, Kenneth	Mechanisms of the Stromal Response to Smoothened Inhibition in Pancreatic Cancer	Columbia University Health Sciences
5R01CA159222-03	Crawford, Howard	ADAM17 in pancreatic cancer and pancreatitis	Mayo Clinic Jacksonville
5R01CA160417-02	Tang, Daolin	Targeting HMGB1-mediated Autophagy in Cancer Therapy	University of Pittsburgh
5R01CA161112-03	Hingorani, Sunil	Overcoming stromal barriers to therapeutics in pancreas cancer	Fred Hutchinson Cancer Research Center
5R01CA161283-02	Grippo, Paul	N-3 Fatty Acid-Induced Akt Suppression: Chemoprevention for Pancreatic Neoplasia	Northwestern University
5R01CA161976-02	Merchant, Nipun	Stat3 Signaling in Pancreas Cancer	Vanderbilt University Medical Center
5R01CA163489-02	Philips, Mark	Characterization of Icmt in Animal Models of Cancer	New York University School of Medicine
5R01CA163649-02	Singh, Pankaj	Targeting MUC1-induced Tumor-stromal Metabolic Cross-talk in Pancreatic Cancer	University of Nebraska Medical Center
5R01CA163698-02	Dyson, Nicholas	Dissection and manipulation of RB function	Massachusetts General Hospital
5R01CA163764-02	Hawkins, William	Sigma-2/Peptidomimetic Conjugates Target Apoptosis In Pancreatic Cancer	Washington University
5R01CA163798-02	Karin, Michael	IKKalpha, autophagy, obesity and injury enhanced pancreatic cancer	University of California, San Diego
5R01CA163895-02	Morgan, Meredith	Selective Sensitization of Pancreatic Cancer to Therapy by Chk1 and PARP1 Inhibit	University of Michigan
5R01CA163907-02	Schwartz, Edward	Interactions of the angiopoietin and PD-ECGF pathways in tumor angiogenesis	Albert Einstein College of Medicine
5R01CA164041-02	Yang, Guang-Yu	Aldo-keto reductase family 1 member B10 AKR1B10 in pancreatic carcinogenesis	Northwestern University
5R01CA168692-02	Cheresh, David	Targeting a non-canonical RAS-driven pathway in pancreatic cancer	University of California, San Diego
5R01CA169123-02	Vonderheide, Robert	Immunobiology and immunotherapy of pancreatic cancer	University of Pennsylvania

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5R01CA170495-02	Cagan, Ross	A Drosophila Model Linking Diet-induced Obesity and Cancer (PQ 1)	Icahn School of Medicine at Mount Sinai
5R01CA170946-02	Saluja, Ashok	Triptolide Augments Death Receptor Mediated Apoptosis in Pancreatic Cancer	University of Minnesota
5R03CA159315-02	Prendergast, George	OPPC targeting to improve pancreatic cancer treatment	Lankenau Institute for Medical Research
5R03CA159383-02	Jolly, Christopher	Omega-3 Fatty Acid Effects on Pancreatitis and Adenocarcinoma Development	University of Texas, Austin
5R03CA164484-02	Sroka, Isis	Mechanisms of Pancreatic Tumor Nerve Invasion	University of Arizona
5R03CA164645-02	Berbeco, Ross	Enhancing tumor vascular damage with gold nanoparticles aided radiation therapy	Dana-Farber Cancer Institute
5R03CA164677-02	Resar, Linda	Targeting the let-7-HMGA2 Network in Metastatic Progression in Pancreatic Cancer	Johns Hopkins University
5R03CA165927-02	Counter, Christopher	Evaluating the impact of KRas codon bias on pancreatic cancer	Duke University
5R03CA166860-02	Livant, Donna	PhScN as a Potent Agent for Use with Radiation in Pancreatic Cancer	University of Michigan
5R03CA167120-02	Li, Ning	Effect of high fat diet on pancreatic cancer in IKKa deficient mice	University of California, San Diego
5R03CA167342-02	Batra, Surinder	Targeting MUC4 for chemosensitization of pancreatic cancer	University of Nebraska Medical Center
5R03CA167471-02	Gamcsik, Michael	PDAC-on-a-Chip for Selection of Aggressive, Therapy-Resistant Tumor Cells	North Carolina State University
5R03CA169829-02	Singh, Seema	ETV4 in pancreatic cancer	University of South Alabama
5R03CA169953-02	Solheim, Joyce	Effect of Beta-secretase Inhibitors on Pancreatic Cancer Cells	University of Nebraska Medical Center
5R21CA155736-02	David, Gregory	Role of cell cycle withdrawal in restricting pancreatic cancer progression.	New York University School of Medicine
5R21CA158640-02	Beachy, Philip	Simultaneous attack of epithelial and stromal compartments in pancreatic cancer	Stanford University
5R21CA158902-02	Wang, Xin	Effectiveness of minocycline for reducing symptoms in pancreatic cancer patients	MD Anderson Cancer Center
5R21CA159240-02	Hingorani, Sunil	Peripheral blood biopsy for molecular diagnosis of pancreatic cancer	Fred Hutchinson Cancer Research Center
5R21CA160293-02	Bogdanov, Vladimir	Tissue Factor splicing and pancreatic tumor progression: pilot studies	University of Cincinnati

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5R21CA161432-03	Guha, Sushovan	Ki-Ras Signaling in Pancreatic Cancer: Role of a Novel Akt Regulator	University of Texas Health Science Center Houston
5R21CA161624-02	Brekken, Rolf	GPCR regulation of progenitor cells in pancreatic cancer	University of Texas Southwestern Medical Center
5R21CA164592-02	Eshleman, James	Identifying Familial Pancreatic Cancer Predisposition Genes	Johns Hopkins University
5R21CA164593-02	Anderson, Karen	Mutation-Specific p53 Antibodies as Biomarkers of Pancreatic Cancer	Arizona State University
5R21CA164690-02	Galbraith, David	Cell-specific analysis of transcription and epigenomic status in PDAC	University of Arizona
5R21CA164795-02	Gross, Kenneth	A novel murine model for metastatic islet cell pancreas cancer	Roswell Park Cancer Institute
5R21CA164880-02	Liu, Yu-Tsueng	Non-invasive sampling of DNA markers for pancreatic cancer screening	University of California, San Diego
5R21CA167092-02	Hu, Yanle	Four-Dimensional MRI for Image-Guided Radiation Therapy for Pancreatic Cancer	Washington University
5R21CA167122-02	Allen, Benjamin	Novel Hedgehog Receptors As Therapeutic Targets In Pancreatic Cancer	University of Michigan
5R21CA167137-02	Singh, Ajay	Myb, a key driver of pancreatic cancer progression and metastasis	University of South Alabama
5R21CA168454-02	Straubinger, Robert	Pancreas cancer combination therapy based on stromal modulators and nano-carriers	State University New York Buffalo
5R21CA169673-02	Attardi, Laura	Elucidating p53 transcriptional networks involved in pancreatic cancer suppression	Stanford University
5R21CA169848-02	Mohammad, Ramzi	Development of Small Molecule Crm-1 Inhibitor for Pancreatic Cancer Therapy	Wayne State University
5R33CA155586-03	Porter, Marc	Advanced Development of a Multiplexed SERS-based Biomarker Detection Platform: A Multiplexed Panel	University of Utah
5R37CA034610-31	Massague, Joan	Transforming Growth Factor-Beta Signal Transduction	Sloan-Kettering Institute for Cancer Research
5R44CA150484-03	Nuccitelli, Richard	EndoPulse System for Endoscopic Ultrasound-Guided Therapy of Pancreatic Carcinoma	Bioelectromed Corporation
5U01CA111294-09	Hollingsworth, Michael	Early Diagnosis of Pancreatic Cancer	University of Nebraska Medical Center
5U01CA111302-09	Killary, Ann	Biomarkers for the Early Detection of Pancreatic Cancer	MD Anderson Cancer Center
5U01CA141468-05	Engleman, Edgar G.	Biology and Immunology of Pancreatic Cancer Stem Cells in a Novel Mouse Model	Stanford University

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5U01CA150138-03	Olson, Sara	Serum IgE and Risk of Pancreatic Cancer	Sloan-Kettering Institute for Cancer Research
5U01CA151650-04	Porter, Marc	Magnetoresistive Sensor Platform for Parallel Cancer Marker Detection	University of Utah
5U01CA151810-04	Yang, Lily	Theranostic Nanoparticles for Targeted Treatment of Pancreatic Cancer	Emory University
5U01CA151886-04	Halas, Nancy	Preclinical platform for theranostic nanoparticles in pancreatic cancer	Rice University
5U01CA151925-05	Kalluri, Raghu	Role of Fibroblasts, Myeloid Cells and Matrix in PDAC	MD Anderson Cancer Center
5U01CA152653-04	Haab, Brian	Detection of Pre-Invasive Pancreatic Cysts Using Protein and Glycan Biomarkers	Van Andel Research Institute
5U01CA166800-02	Cullen, Joseph	Ascorbate-Induced Radiosensitization in Pancreatic Cancer	University of Iowa
5U01CA168896-02	Haab, Brian	Targeted Glycomics and Affinity Reagents for Cancer Biomarker Development	Van Andel Research Institute
5U54CA163120-03	Batra, Surinder	Pancreatic Tumor Micro-environment Network	University of Nebraska Medical Center
7R01CA135011-06	Mukherjee, Priyabrata	Development of a gold nanoparticles based targeted delivery system	University of Oklahoma Health Sciences Center
7R01CA142736-05	Chauhan, Subhash	Aspects of MUC13 Mucin in Cancer	University of Tennessee Health Science Center
7R01CA163541-02	Powis, Garth	Exploiting tumor stroma interactions for cancer therapy	Sanford-Burnham Medical Research Institute
7U01CA151455-04	Lin, Wenbin	Nanoscale Metal-organic Frameworks for Imaging and Therapy of Pancreatic Cancer	University of Chicago
N43CO130060-000	Scholz, Wolfgang	SBIR Phase I Topic 324: Development of an Imaging Agent Targeting Sialyl Lewis A	Mabvax Therapeutics, Inc.
N44CO130071-000	Hupert, Mateusz	SBIR Phase II: Low-Cost Microfluidic System for Detection of CTCs	Biofluidica Microtechnologies LLC
ZIA BC 011162	Hussain, S. Perwez	Integrative Molecular Profiling of Human Pancreatic Cancer	NCI
ZIA BC 011185	Hussain, S. Perwez	Role of Immune and Inflammation Mediators in Progression of Pancreatic Cancer	NCI
ZIA BC 011267	Rudloff, Udo	Preclinical drug development in pancreatic cancer	NCI
ZIA BC 011416	Westlake, Christopher	Investigation of Rabs and trafficking regulators roles in tumorigenesis	NCI
ZIA BC 011463	Van Dyke, Terry	Adoption and Retooling of GEM model for Pancreatic Cancer	NCI

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ZIA BC 011485	Hussain, S. Perwez	Forkhead-box (FOX) Transcription Factors in the Progression of Pancreatic Cancer	NCI
ZIA BC 011526	Van Dyke, Terry	Therapeutic evaluation in GEM pancreatic model	NCI
ZIA CP010193-10392	Solomon, Rachael	PanScan - Genome Wide Scan of Pancreatic Cancer	NCI
ZIA CP010202-10378	Solomon, Rachael	PLCO Pancreas Cancer	NCI
5P50CA062924-20	Kern, Scott	SPORE in Gastrointestinal Cancer	Johns Hopkins University
5K07CA140390-06	Innocenti, Federico	Genome-Wide molecular epidemiology of treatment outcome and cancer risk	University of North Carolina at Chapel Hill
ZIA CP010201-10569	Amundadottir, Laufey	LTG_Amundadottir	NCI
5P01CA084203-10	Hasan, Tayyaba	Molecular Response and Imaging-based Combination Strategies for Optimal PDT	Massachusetts General Hospital
3P50CA130810-04S1	Brenner, Dean	Translational Research in GI Cancer	University of Michigan
5P50CA130810-04	Brenner, Dean	Translational Research in GI Cancer	University of Michigan
1F31CA180602-01	Hesler, Rachel	The Role of Type III TGF-beta Receptor in the Fibrotic Tumor Stroma	Duke University
1R01CA172560-01	Gozani, Or	Mechanisms of action of the Smyd3 methyltransferase in cancer cells	Stanford University
1R01CA174294-01A1	Wu, Anna	Multifunctional immunoPET tracers for pancreatic and prostate cancer	University of California, Los Angeles
2R01CA051210-21	Ross, David	Biochemical and molecular studies on NQO1. Design of less toxic Hsp90 inhibitors	University of Colorado
2R44CA168158-02	Krasnoperov, Valery	Development of sEphB4-HSA as Novel Therapeutic in Cancer	Vasgene Therapeutics, Inc.
3R41CA174059-01S1	Piermarocchi, Carlo	Search Algorithms for Drug Combinations: Extending Approved Cancer Therapies	Salgomed, Inc.
4R01CA106456-10	Vlodavsky, Israel	Regulation of heparanase in cancer progression	Technion-Israel Institute of Technology
5F30CA167910-02	Tsai, Frederick	K-Ras4A Trafficking and Signaling	New York University School of Medicine
5R00CA149182-05	Maher, Christopher	Characterization of Cancer Transcriptomes using Next Generation Sequencing	Washington University
5R01CA065910-17	Cance, William	Focal Adhesion Kinase - Tumor Biology and Therapeutics	Roswell Park Cancer Institute
5R01CA078814-15	Sporn, Michael	New Triterpenoids for Chemoprevention and Therapy of Cancer	Dartmouth College
5R01CA095137-10	Lanier, Lewis	NK Cell Biology	University of California, San Francisco

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5R01CA139599-05	Allbritton, Nancy	Multiplexed Measurement of Kinase Activity in Single Cancer Cells	University of North Carolina at Chapel Hill
5R01CA142669-04	Bouvet, Michael	Fluorophore-Conjugated Antibodies for Imaging and Resection of GI Tumors	University of California, San Diego
5R01CA154586-02	Wang, Xiao-Fan	The anti-senescence activity of trefoil factor 1	Duke University
5R01CA160924-03	De Lange, Titia	The role of telomere-related tetraploidization in cancer	Rockefeller University
5R01CA167174-02	Sugahara, Kazuki	The role of fibroblasts in the activities of tissue penetrating peptides	Sanford-Burnham Medical Research Institute
5R01CA170911-02	Libutti, Steven	Deciphering the Tissue Specificity of MEN1 Related Tumorigenesis	Albert Einstein College of Medicine
5R21CA143362-03	Messmer, Bradley	Molecular Evolution of Multifunctional DNA Nanoparticles	University of California, San Diego
5U01CA128454-07	Pierce, James	Discovery and Development of Cancer Glycomarkers	University of Georgia
7R01CA151374-04	Martin, Lainie	Evaluation of In Vivo Optical Imaging in Pancreatic and Ovarian Cancer Patients	Research Institute of Fox Chase Cancer Center
7R01CA167174-03	Sugahara, Kazuki	The role of fibroblasts in the activities of tissue penetrating peptides	Columbia University Health Sciences
ZIA BC 010451	Barchi, Joseph	Carbohydrate Antigen-bearing Nanoparticles for Anti-adhesives and Tumor Vaccines	NCI
ZIA BC 010774	Ashwell, Jonathan	T Cell Alternative p38 Activation Pathway	NCI
5U54CA151668-04	Gorenstein, David	Texas Center for Cancer Nanomedicine	University of Texas Health Science Center, Houston
3U54CA132379-05S1	Martinez, Maria	Comprehensive SDSU-UCSD Cancer Center Partnership (2 of 2)	University of California, San Diego
2R01CA045726-26A1	Cheresh, David	Integrin alpha v beta 3 promotes resistance to EGF receptor inhibitors	University of California, San Diego
3U54CA132384-05S2	Klonoff, Elizabeth	Comprehensive SDSU/UCSD Cancer Center Partnership 1 of 2	San Diego State University
5F32CA163092-02	Bayrer, James	LRH-1: Structure-based Approach to Drug Design for Gastrointestinal Tumors	University of California, San Francisco
1R21CA181859-01	Wang, Zhenghe	Next-generation mouse gene-targeting technology to model tumorigenesis	Case Western Reserve University
1U01CA176303-01	Kemp, Christopher	An integrated computational and functional genomics discovery engine for preclinically validated cancer drug targets	Fred Hutchinson Cancer Research Center
3R01CA133697-04S1	Tamanoi, Fuyuhiko	Nanovalve Platform: Targeted, Controlled, Release of Anticancer Drugs	University of California, Los Angeles

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5K01CA172957-02	Blind, Raymond	Cancer cell signaling through lipids complexed to proteins	University of California, San Francisco
5K24CA113433-09	Syngal, Sapna	The Genetics and Prevention of Gastrointestinal Cancers	Dana-Farber Cancer Institute
5R00CA149169-04	Singh, Anurag	Defining lineage-specific determinants of K-Ras “addiction” in human cancers	Boston University Medical Campus
5R01CA067267-19	Johnson, Candace	Anti-Tumor Mechanisms and Therapeutic Effects of Vitamin D	Roswell Park Cancer Institute
5R01CA116034-08	Philips, Mark	Regulation of K-Ras by a Farnesyl-electrostatic Switch	New York University School of Medicine
5R01CA118005-06	Altieri, Dario	Rational Design and Clinical Development of Shepherdin: A Novel Anti-Cancer Agent	Wistar Institute
5R01CA133697-04	Tamanoi, Fuyuhiko	Nanovalve Platform: Targeted, Controlled, Release of Anticancer Drugs	University of California, Los Angeles
5R01CA163441-02	Strober, Samuel	Radiotherapy as Immunotherapy of Tumors	Stanford University
5R01CA169774-02	Pagel, Mark	Detection of in vivo enzyme activities with CEST MRI	University of Arizona
5R37CA050286-25	Cheresh, David	VEGF and PDGF in angiogenesis and tumor progression	University of California, San Diego
5U01CA141457-05	Pandolfi, Pier Paolo	The Co-Clinical Trial Project	Beth Israel Deaconess Medical Center
3U54CA163111-03S1	Wang, Timothy	Myofibroblasts in Gastrointestinal Cancers	Columbia University Health Sciences
5R01CA135328-04	Mahajan, Nupam	Ack1: A Critical Regulator of Hormone-Refractory Prostate Cancer	H. Lee Moffitt Cancer Center & Research Institute
5R01CA155332-03	Ivan, Mircea	Role of Hypoxia-Induced miR-210 in Tumor Metabolism	Indiana University–Purdue University Indianapolis
5U54CA163111-03	Wang, Timothy	Myofibroblasts in Gastrointestinal Cancers	Columbia University Health Sciences
ZIA BC 010649	Kammula, Udai	Immunotherapy Strategies for Gastrointestinal and Hepatocellular Cancer	NCI
ZIA BC 011343	Greten, Tim	Clinical protocols for the treatment of gastrointestinal cancer	NCI
2P01CA067166-16A1	Giaccia, Amato	Tumor Hypoxia: Molecular Studies and Clinical Exploitation	Stanford University
1R01CA169134-01A1	Amaravadi, Ravi	HLTF gene silencing: a novel determinant of sensitivity to autophagy inhibition	University of Pennsylvania
3R25CA153915-04S1	Mattrey, Robert	UCSD Cancer Nanotechnology Training Center	University of California, San Diego
3R41CA174089-02S1	Schlosser, Jeffrey	Robotic Ultrasound Image Guidance System for Radiation Therapy	Sonitrack Systems, Inc.

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5P01CA080124-12	Jain, Rakesh	Integrative Pathophysiology of Solid Tumors	Massachusetts General Hospital
5R01CA103314-22	Ojima, Iwao	Tumor-Targeting Chemotherapeutic Agents	State University of New York at Stony Brook
5R01CA112314-08	Yarema, Kevin	Mechanism and Anti-Cancer Activity of SCFA-Hexosamine Analogs	Johns Hopkins University
5R01CA120409-07	June, Carl	Immunotherapy with Car T Cells	University of Pennsylvania
5R01CA142637-04	Rosenthal, Eben	CD147 as a Novel Target in Head and Neck Cancer	University of Alabama at Birmingham
5R01CA155117-03	Parsons, Ramon	Mutual Regulation of PTEN and P-REX2a in Normal and Cancer Cells	Columbia University Health Sciences
5R01CA161613-03	Wong, John	Integrated 3D X-Ray/ultrasound guided radiation therapy of soft tissue targets	Johns Hopkins University
5R25CA153915-04	Mattrey, Robert	UCSD Cancer Nanotechnology Training Center	University of California, San Diego
5R41CA174089-02	Schlosser, Jeffrey	Robotic Ultrasound Image Guidance System for Radiation Therapy	Sonitrack Systems, Inc.
7R01CA155117-04	Parsons, Ramon	Mutual Regulation of PTEN and P-REX2a in Normal and Cancer Cells	Icahn School of Medicine at Mount Sinai
7U01CA105492-10	Holland, Eric	Using mouse models to probe the relationship of oncogenesis to development and oncogene dependence	Fred Hutchinson Cancer research Center
ZIA BC 011344	Greten, Tim	Immune suppressor mechanisms in patients with GI cancer	NCI
ZIA BC 011411	Van Dyke, Terry	Development of ES/iPSC approach for non-germline GEM modeling	NCI
ZIA CP010136-00430	Silverman, Debra	Black/White PHS Study	NCI
ZIA CP010197-10542	Moore, Steven	Metabolomics of energy balance, nutritional status, and cancer	NCI
ZIA CP010219-10435	Berrington, Amy	Cohort Consortium BMI Pooling Project	NCI

FY 2013 NCI Grants Related to SCLC

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1R21CA169979-01A1	Haura, Eric B.	Activity-Based Kinase Discovery in Small Cell Lung Cancer	H. Lee Moffitt Cancer Center & Research Institute
1U01CA176284-01	Roth, Michael G.	Lung cancer oncogenotype-selective drug target discovery	University of Texas Southwestern Medical Center
3P50CA058187-18S1	Bunn, Paul A.	SPORE in Lung Cancer	University of Colorado
3P50CA070907-15S1	Minna, John D.	University of Texas SPORE in Lung Cancer	University of Texas Southwestern Medical Center
5F32CA165856-02	Nicolay, Brandon	Understanding the role of SKP2 in small cell lung cancer progression	Massachusetts General Hospital
5K23CA164015-03	Owonikoko, Taofeek K.	Novel systemic therapy to improve clinical outcome in small cell lung cancer	Emory University
5P50CA058184-18	Baylin, Stephen B.	SPORE in Lung Cancer	Johns Hopkins University
5R01CA131217-05	Oyelere, Adegboyega	Nonpeptide macrocyclic histone deacetylase (HDAC) inhibitors for targeted lung cancer treatment	Georgia Institute of Technology
5R01CA136534-04	Deng, Xingming	Structure-based anti-cancer drug development	Emory University
5R44CA162613-03	Pang, Roy H.L.	Targeted Treatment of Recurrent Small Cell Lung Cancer with Anti-AbnV2 Antibodies	Woomera Therapeutics, Inc.
ZIA SC 000167	Linnoila, Ilona	Molecular Pathology of Pulmonary Carcinogenesis	NCI
ZIA SC 010093	Schrump, David	Targeting the Epigenome for Lung Cancer Therapy	NCI
1R44CA174074-01A1	Strum, Jay Copeland	Development of GZ38-1, a Novel Protectant of Chemotherapy-Induced Myelosuppression	G1 Therapeutics, Inc.
5R01CA148867-05	Macpherson, David	Using mouse models to understand retinoblastoma initiation and progression	Fred Hutchinson Cancer Research Center
ZIC BC 011040	Edelman, Dan	Molecular Profiling of Clinical Specimens	NCI

Appendix I: Funding for Chronic Diseases and Organ Systems

More information on NIH Categorical Spending is available here

http://report.nih.gov/categorical_spending.aspx

Research Areas	FY 2012 (in millions)	FY 2013 (in millions)
Auditory System[794]		
Otitis Media	$17	$14
Brain Disorders	$3,968	$3,708
ALS	$44	$39
Alzheimer's Disease	$503	$504
Aphasia	$24	$24
Autism	$192	$186
Batten Disease	$4	$5
Brain Cancer	$281	$280
Cerebral Palsy	$42	$18
Epilepsy	$156	$129
Frontotemporal Dementia (FTD)	$26	$32
Pick's Disease	$2	$3
Huntington's Disease	$65	$55
Intellectual and Developmental Disabilities	$355	$343
Autism	$192	$186
Down Syndrome	$20	$18
Fragile X Syndrome	$27	$30
Fetal Alcohol Syndrome	$32	$33
Multiple Sclerosis	$115	$112
Parkinson's Disease	$154	$135
Rett Syndrome	$13	$13
Reye's Syndrome	$0	$0
Schizophrenia	$268	$232
Tourette Syndrome	$6	$4
Traumatic Brain Injury	$79	$88
Tuberous Sclerosis	$23	$20
Cancer	$5,621	$5,274
Brain Cancer	$281	$280
Breast Cancer	$800	$657
Cervical Cancer	$112	$98

[794] Note that this is not designated as a NIH Research, Condition, and Disease Category and therefore does not have an official annual funding amount aligned with it in the NIH Categorical Spending data.

Research Areas	FY 2012 (in millions)	FY 2013 (in millions)
Childhood Leukemia	$77	$67
Colorectal Cancer	$302	$281
HPV and/or Cervical Cancer Vaccine	$26	$25
Liver Cancer	$73	$71
Lung Cancer	$233	$208
Lymphoma	$213	$233
Hodgkin's Disease	$21	$13
Neuroblastoma	$34	$33
Ovarian Cancer	$147	$133
Pancreatic Cancer	$127	$125
Prostate Cancer	$257	$286
Uterine Cancer	$42	$39
Cardiovascular	**$2,040**	**$1,964**
Atherosclerosis	$477	$374
Heart Disease	$1,278	$1,230
Coronary Heart Disease	$468	$404
Hypertension	$215	$222
Chronic Fatigue Syndrome	**$5**	**$5**
Dental/Oral and Craniofacial Disease	**$516**	**$480**
Temporomandibular Muscle/Joint Disorder (TMJD)	$21	$19
Diabetes	**$1,061**	**$1,007**
Digestive Diseases	**$1,719**	**$1,575**
Gallbladder Infection	$11	$10
Peptic Ulcer	$20	$19
Inflammatory Bowel Disease	$121	$114
Crohn's Disease	$76	$61
Colorectal Cancer	$302	$281
Liver Diseases	$632	$594
Chronic Liver Disease and Cirrhosis	$288	$282
Liver Cancer	$73	$71
Hepatitis	$210	$195
Hepatitis A	$2	$2
Hepatitis B	$51	$48
Hepatitis C	$112	$101
Endocrine System[788]		
Estrogen	$221	$218
Diethylstilbestrol (DES)	$3	$1
Eye Disease and Disorders of Vision	**$841**	**$774**
Macular Degeneration	$101	$98

Research Areas	FY 2012 (in millions)	FY 2013 (in millions)
Hematology	$1,091	$1,020
Childhood Leukemia	$77	$67
Cooley's Anemia	$20	$15
Septicemia	$96	$88
Sickle Cell Disease	$65	$70
Immune System[788]		
Allergic Rhinitis (Hay Fever)	$7	$9
Asthma	$229	$207
Autoimmune Disease	$867	$821
Inflammatory Bowel Disease	$121	$114
Lupus	$108	$92
Multiple Sclerosis	$115	$112
Myasthenia Gravis	$7	$7
Psoriasis	$10	$12
Scleroderma	$24	$21
Childhood Leukemia	$77	$67
Food Allergies	$31	$36
Lymphoma	$213	$233
Hodgkin's Disease	$21	$13
Vaccine-Related	$1,691	$1,608
AIDS (vaccine)	$557	$518
Biodefense	$1,791	$1,692
HPV and/or Cervical Cancer Vaccine	$26	$25
Malaria Vaccine	$40	$34
Tuberculosis Vaccine	$21	$26
Integumentary System[788]		
Psoriasis	$10	$12
Scleroderma	$24	$21
Lung	$1,286	$1,230
Acute Respiratory Distress Syndrome	$98	$95
Asthma	$229	$207
Chronic Obstructive Pulmonary Disease	$101	$102
Cystic Fibrosis	$86	$78
Emphysema	$20	$24
Lung Cancer	$233	$208
Perinatal/Neonatal Respiratory Distress Syndrome	$38	$33
Pneumonia	$115	$113
Mental Health	$2,287	$2,174
Autism	$192	$186
Attention Deficit Disorder (ADD)	$60	$49
Depression	$429	$415
Schizophrenia	$268	$232

Research Areas	FY 2012 (in millions)	FY 2013 (in millions)
Musculoskeletal System[788]		
Skeletal Muscle[788]		
Muscular Dystrophy	$75	$76
Myotonic Dystrophy	$10	$10
Duchenne/Becker Muscular Dystrophy	$34	$33
Facioscapulohumeral Muscular Dystrophy	$5	$5
Myasthenia Gravis	$7	$7
Spinal Muscular Atrophy	$15	$13
Skeletal System[788]		
Osteogenesis Imperfecta	$9	$8
Osteoporosis	$181	$164
Paget's Disease	$1	$0
Joints, Ligaments, and Connective Tissues[788]		
Temporomandibular Joint and Muscle Disorder (TMJD)	$21	$19
Neurosciences	$5,618	$5,340
Pain Research[788]		
Fibromyalgia	$13	$11
Headaches	$24	$25
Migraines	$18	$19
Pain Conditions — Chronic	$396	$402
Vulvodynia	$4	$4
Renal System		
Kidney Disease	$556	$551
Polycystic Kidney Disease	$42	$40
Urologic Diseases	$496	$497
Interstitial Cystitis	$10	$10
Prostate Cancer	$257	$286
Reproductive System[788]		
Cervical Cancer	$112	$98
Ovarian Cancer	$147	$133
Prostate Cancer	$257	$286
Uterine Cancer	$42	$39
Vulvodynia	$4	$4
Adolescent Sexual Activity	$76	$70
Teenage Pregnancy	$18	$17
Contraception/Reproduction	$448	$408
Endometriosis	$9	$7
Fibroid Tumors (Uterine)	$14	$10
Infertility	$74	$78

Appendix J: Acronyms

ACC	Autism Coordinating Committee
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Autism Centers of Excellence
AD	Alzheimer's disease
ADCG	Alzheimer's Disease Genetics Consortium
ADCS	Alzheimer's Disease Cooperative Study
ADC	Alzheimer's disease center
ADD	attention deficit disorder
Add Health	National Longitudinal Survey of Adolescent to Adult Health
ADDM	Autism and Developmental Disabilities Monitoring
ADEAR	Alzheimer's Disease Education and Referral Center
ADHD	attention deficit hyperactivity disorder
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADSP	Alzheimer's Disease Sequencing Project
AEIO	Autism Evaluation Implementation Oversight
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
ALD	alcoholic liver disease
ALS	amyotrophic lateral sclerosis
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
Army STARRS	Army Study to Assess Risk and Resiliences in Servicemembers
ARS	acute radiation syndrome
ART	antiretroviral therapy
ASD	autism spectrum disorder
ASNHL	autoimmune sensorineural hearing loss
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
BAER	Basal Adverse Event Report
BARDA	Biomedical Advanced Research and Development Authority
BCERP	Breast Cancer and the Environment Research Program
BCHE	butyrylcholinesterase
BCI	brain–computer interface
BD2K	Big Data to Knowledge
BLSA	Baltimore Longitudinal Study of Aging
BMD	Becker muscular dystrophy
BMD	bone mineral density
BMMSC	bone marrow mesenchymal stem cell
BMSC	bone marrow stromal cell
BPA	bisphenol A

BPH	benign prostatic hyperplasia
BRAIN	Brain Research through Advancing Innovative Neurotechnologies
BSL	biosafety level
BTR	Biomedical Technology Resource
BTRC	Biomedical Technology Resource Center
BTRR	Biomedical Technology Research Resource
CADET	Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Disease
CBIIT	Center for Biomedical Informatics and Information Technology
CC	NIH Clinical Center
CCOP	Community Clinical Oncology Program
CDC	Centers for Disease Control and Prevention
CEIRS	Centers of Excellence for Influenza Research and Surveillance
CER	comparative effectiveness research
CEST	Chemical Exchange Saturation Transfer
CF	cystic fibrosis
CFS	chronic fatigue syndrome
CFTR	cystic fibrosis transmembrane conductance regulator
CHARGE	Childhood Autism Risks from Genetics and Environment
CHD	congenital heart disease
CHI	Center for Human Immunology, Autoimmunity, and Inflammation
CISNET	Cancer Intervention and Surveillance Modeling Network
CIT	Center for Information Technology
CKD	chronic kidney disease
CLARITY	Clear Lipid-exchanged Anatomically Rigid Imaging/immunostaining-compatible Tissue hYdrogel
CMD	congenital muscular dystrophy
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
COE	center of excellence
COPD	chronic obstructive pulmonary disease
CounterACT	Countermeasures Against Chemical Threats
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CPEA	Collaborative Programs of Excellence in Autism
CPTAC	Clinical Proteomic Tumor Analysis Consortium
CRIC	Chronic Renal Insufficiency Cohort
CRISPR	clustered regularly interspaced short palindromic repeats
CRN	Cancer Research Network
CSER	Clinical Sequencing Exploratory Research
CSF	cerebrospinal fluid
CSR	Center for Scientific Review
CT	computed tomography
CTD2	Cancer Target Discovery and Development
CTN	Clinical Trials Network

CTSA	Clinical and Translational Science Awards
CURE	Continuing Umbrella of Research Experiences
CVD	cardiovascular disease
DAD	diabetes and deafness
DARPA	Defense Advanced Research Projects Agency
dbGAP	database of Genotypes and Phenotypes
DEBUT	Design by Biomedical Undergraduate Teams
DES	diethylstilbestrol
DMCC	Data Management and Coordinating Center
DMD	Duchenne muscular dystrophy
DME	diabetic macular edema
DNA	deoxyribonucleic acid
DoD	U.S. Department of Defense
DoE	U.S. Department of Energy
DOHaD	Developmental Origins of Health and Disease
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DPP	Diabetes Prevention Program
DSLD	Dietary Supplement Label Database
E. coli	*Escherichia coli*
EARLI	Early Autism Risk Longitudinal Investigation
ED	Department of Education
EDRN	Early Detection Research Network
EDTA	ethylene diamine tetra-acetic acid
ELGANs	extremely low gestational age neonates
eMERGE	Electronic Medical Records and Genomics
EMR	electronic medical record
ENaC	epithelial sodium channel
ENCODE	Encyclopedia of DNA Elements
EOL PC	end-of-life and palliative care
EPA	U.S. Environmental Protection Agency
Epo	erythropoietin
EPR	Environmental Polymorphisms Registry
eRA	Electronic Research Administration
FASD	fetal alcohol spectrum disorder
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007
FDAMA	FDA Modernization Act of 1997
FIC	John E. Fogarty International Center
FITBIR	Federal Interagency Traumatic Brain Injury Research
fMRI	functional magnetic resonance imaging
FNLCR	Frederick National Laboratory for Cancer Research
FOA	Funding Opportunity Announcement
FSHD	facioscapulohumeral muscular dystrophy
FY	fiscal year
GA	geographic atrophy
GBM	glioblastoma multiforme
GI	gastrointestinal
GPCR	G-protein coupled receptor

GPRA	Government Performance and Results Act
GSIG	GeroScience Interest Group
GVHD	graft-versus-host disease
GWAS	genome-wide association study
HAART	highly active antiretroviral therapy
HANDLS	Healthy Aging in Neighborhoods of Diversity across the Life Span
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
hESC	human embryonic stem cell
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMO	health maintenance organization
HMP	Human Microbiome Project
HPV	human papillomavirus
HRS	Health and Retirement Study
HSCT	hematopoietic stem cell transplantation
IACC	Interagency Autism Coordinating Committee
IADRP	International Alzheimer's Disease Research Portfolio
IARC	International Agency for Research on Cancer
IBCERCC	Interagency Breast Cancer and Environmental Research Coordinating Committee
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	Institute or Center
IC/PBS	interstitial cystitis/painful bladder syndrome
ICBP	Integrative Cancer Biology Program
ICER	International Centers for Excellence in Research
IDeA	Institutional Development Award
IDP	individual development plan
IGI	image-guided intervention
IMAT	Innovative Molecular Analysis Technologies
IND	investigational new drug
IPRCC	Interagency Pain Research Coordinating Committee
iPSC	induced pluripotent stem cell
IRB	institutional review board
IRP	Intramural Research Program
ISS	International Space Station
ITP	Interventions Testing Program
JJ-TRIALS	Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System
LGMD	limb-girdle muscular dystrophy
LMICs	low- and middle-income countries
MACS	Multicenter AIDS Cohort Study
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MCP	Microbiome Cloud Project

MD	muscular dystrophy
MD-CARE	Muscular Dystrophy Community Assistance, Research, and Education Amendments
MDR	multidrug-resistant
MEG	magnetoencephalography
MESA	Multi-Ethnic Study of Atherosclerosis
mHealth	mobile health
MHRN	Mental Health Research Network
MIDAS	Models of Infectious Disease Agent Study
MIDUS	Mid-Life in the U.S. (MIDUS) project
MIRAS	mitochondrial recessive ataxia syndrome
MJD	Machado–Joseph disease
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MRI/S	magnetic resonance imaging and spectroscopy
MS	multiple sclerosis
Mtb	*Mycobacterium tuberculosis*
MTCT	mother-to-child transmission
MTF	Monitoring the Future
NACC	National Alzheimer's Coordinating Center
NAPA	National Alzheimer's Project Act
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NASH	nonalcoholic steatohepatitis
NCATS	National Center for Advancing Translational Sciences
NCBI	National Center for Biotechnology Information
NCCAM	National Center for Complementary and Alternative Medicine
NCCCP	National Community Cancer Centers Program
NCCIH	National Center for Complementary and Integrative Health
NCCOR	National Collaborative on Childhood Obesity Research
NCI	National Cancer Institute
NCIG	NIAAA's Clinical Investigations Group
NCIP	National Cancer Informatics Program
NCORP	National Community Oncology Research Program
NCRAD	National Cell Repository for Alzheimer's Disease
NCRR	National Center for Research Resources
NCTN	National Clinical Trials Network
NDAR	National Database for Autism Research
NDEP	National Diabetes Education Program
NDFW	National Drug Facts Week
NEHEP	National Eye Health Education Program
NEI	National Eye Institute
NEIGHBOR	NEI Glaucoma Human genetics collaBORation
NETT	Neurological Emergencies Treatment Trials
NeuroNEXT	Network for Excellence in Neuroscience Clinical Trials
NExT	NCI Experimental Therapeutics

NHANES	National Health and Nutrition Examination Study
NHATS	National Health and Aging Trends Study
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NHOPI	Native Hawaiian and Other Pacific Islander
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
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
NITRC	Neuroimaging Informatics Tools and Resources Clearinghouse
NLM	National Library of Medicine
NLST	National Lung Screening Trial
NMRI	Network of Minority Health Research Investigators
NRFC	not recommended for further consideration
NRSA	National Research Service Award
NSF	National Science Foundation
NSSP	National Strategy for Suicide Prevention
NTP	National Toxicology Program
OAIC	Claude D. Pepper 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
OER	Office of Extramural Research
OIR	Office of Intramural Research

OPPERA	Orofacial Pain Prospective Evaluation and Risk Assessment Study
OppNet	Basic Behavioral and Social Science Opportunity Network
ORDR	Office of Rare Diseases Research
ORIP	Office of Research Infrastructure Programs
ORWH	Office of Research on Women's Health
P–12	pre-kindergarten to grade 12
P5	Pox-Protein Public-Private Partnership
PA	program announcement
PASS	Prenatal Alcohol and SIDS and Stillbirth
PATH	Population Assessment of Tobacco and Health
PBRN	Practice-Based Research Network
PCBC	Progenitor Cell Biology Consortium
PCO	patient-centered outcome
PCR	polymerase chain reaction
PD	Parkinson's disease
PDAC	pancreatic ductal adenocarcinoma
PEPFAR	President's Emergency Plan for AIDS Relief
PEPH	Partnerships for Environmental Public Health
PET	positron emission tomography
PGC	Psychiatric Genomics Consortium
PGRN	Pharmacogenomics Research Network
PHACS	Pediatric HIV/AIDS Cohort Study
PharmGKB	Pharmacogenomics Knowledgebase
PHS	Public Health Service
PMC	PubMed Central
POCTRN	Point-of-Care Technologies Research Network
PQ	Provocative Questions
PROMIS	Patient Reported Outcomes Measurement Information System
PSM	phenol-soluble modulin
PS-ON	Physical Sciences-Oncology Network
PTSD	post-traumatic stress disorder
PumpKIN	Pumps for Kids, Infants, and Neonates
QIBA	Quantitative Imaging Biomarkers Alliance
QIN	Quantitative Imaging Network
R&D	research and development
RA	rheumatoid arthritis
rAd	recombinant adenovirus
RAISE	Recovery After an Initial Schizophrenia Episode
RAPID	Rapidly-Acting Treatments for Treatment-Resistant Depression
RDCRN	Rare Diseases Clinical Research Network
RDoC	Research Domain Criteria
REMBRANDT	REpository of Molecular BRAin Neoplasia DaTa
RFA	request for applications
RNA	ribonucleic acid
ROP	retinopathy of prematurity
RP	retinitis pigmentosa
RPE	retinal pigment epithelium

RPTF Research Prioritization Task Force

SAMHSA Substance Abuse and Mental Health Services Administration

SAMMPRIS Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis

SBIR Small Business Innovation Research

SCA3 spinocerebellar ataxia type 3

SCD sickle cell disease

SCLC small cell lung cancer

SCSU Special Clinical Studies Unit

SDH complex II

SEER Surveillance Epidemiology and End Results

SEPA Science Education Partnership Award

SES socioeconomic status

SIDS sudden infant death syndrome

SLE systemic lupus erythematosus

SMI serious mental illness

SMILE in CARING for YOUTH Strategic Multisite Initiative for the Identification, Linkage, and Engagement in Care of Youth with Undiagnosed HIV Infection

SPIROMICS SubPopulations and InteRmediate Outcome Measures In COPD Study

SPORE Specialized Program of Research Excellence

SRG Scientific Review Group

STAART Studies to Advance Autism Research and Treatment

STI sexually transmitted infection

STTR Small Business Technology Transfer

SUD substance use disorder

SUI stress urinary incontinence

TAA thoracic aortic aneurysm

TAILORx Trial Assigning IndividuaLized Options for Treatment

TALEN transcription activator-like effector nucleases

TARGET Therapeutically Applicable Research to Generate Effective Treatments

TB tuberculosis

TBI traumatic brain injury

TCC Transdisciplinary Collaborative Centers for Health Disparities Research

TCGA The Cancer Genome Atlas

TCIA The Cancer Imaging Archive

TGF-beta transforming growth factor beta

TMAO trimethylamine N-oxide

TMD temporomandibular joint and muscle disorder

TODAY Treatment Options for Type 2 Diabetes in Adolescents and Youth

Treg cells T-regulatory cells

TrialNet Type 1 Diabetes TrialNet

TS Tourette syndrome

TSC tuberous sclerosis complex

UCLA University of California, Los Angeles

UCSD	University of California, San Diego
UDP	Undiagnosed Diseases Program
UI	urinary incontinence
UMLS	Unified Medical Language System
UNC	University of North Carolina
USDA	U.S. Department of Agriculture
USPSTF	U.S. Preventive Services Task Force
UTI	urinary tract infection
VA	U.S. Department of Veterans Affairs
VRC	Vaccine Research Center
VTEUs	Vaccine and Treatment Evaluation Units
We Can!	Ways to Enhance Children's Activity and Nutrition
Wellstone MDCRC	Paul D. Wellstone Muscular Dystrophy Cooperative Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WNV	West Nile virus
WTP	Superfund Worker Training Program
XDR	extensively drug-resistant