Report of the Director

National Institutes of Health

Fiscal Years 2010 & 2011

NIH National Institutes of Health
Turning Discovery Into Health

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Preface

This is the third National Institutes of Health (NIH) Biennial Report submitted under the requirement established by Section 104 of the NIH Reform Act (Pub. L. No. 109-482). Appendix A provides the language in the Reform Act that is relevant to this report, along with the language of two subsequent laws that supplement the provisions of the Reform Act—the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85) and the Newborn Screening Saves Lives Act of 2007 (Pub. L. No. 110-204). NIH's goal is for the information in this report to serve as a useful reference for understanding NIH activities and operations and welcomes feedback on the report.

Chapter Organization

Chapter 1 opens with a statement from the Director of the NIH providing an assessment of 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 topics covered include:

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

The chapter begins with a brief introduction that describes the full continuum of biomedical research at NIH. The research continuum begins with basic research, moves onto early or preclinical translational research, then goes into clinical research, proceeds to translational research, and ends with clinical and community practice. 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 across all of the Institutes and Centers (ICs) and Office of the Director (OD) program offices. Specific examples are included in the summary, illustrating 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. Effective communication activities are another important facet of NIH's mission. Targeted health communication plans and information campaigns that provide science-based information are essential to improving people's health and saving lives. Chapter 2 concludes with NIH-funded research technologies, which provide innovative tools that are used within multiple steps in the continuum and often provide the means for an exchange of information.

Chapter 3 addresses NIH research activities from the perspective of diseases, disorders, and adverse health conditions. The topics covered include:

- Cancer
- Neuroscience and Disorders of the Nervous System
- Life Stages, Human Development, and Rehabilitation
- Chronic Diseases and Organ Systems
- Autoimmune Diseases
- Infectious Diseases and Biodefense
- Minority Health and Health Disparities

These topics, all categories specified in the NIH Reform Act of 2006 (see Appendix A), are grouped together in one chapter to address the intent of the statute, in terms of presenting information on diseases, disorders, and adverse health conditions in a standardized format. Each topic is addressed in a separate section.

Chapter 4 addresses certain NIH Centers of Excellence. Overall, NIH Centers of Excellence 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 the fiscal year (FY) 2010 and 2011 biennial period (covering programmatic and research activities and outcomes), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in the order of their establishment:

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

The *Appendices* present reference documents and supporting data. Appendix A provides a copy of the sections of the NIH Reform Act of 2006 (Pub. L. No. 109-482) that require this Biennial Report, as well as the relevant text from two subsequent laws that supplement the provisions of the Reform Act—the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85) and the Newborn Screening Saves Lives Act of 2007 (Pub. L. No. 110-204). Appendix B lists and provides links to the missions and strategic plans of the NIH ICs and the missions of the OD program offices. Appendix C provides the Common Fund Strategic Planning Report of 2011. Appendix D provides excerpts of *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research* as required by the NIH Reform Act of 2006, in order to identify clinical research study populations and ensure the scientifically appropriate inclusion of individuals according to sex/gender, race, and ethnicity. 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 provides excerpts of the *Report of the Advisory Committee on Research on Women's Health*, in order to include, by reference, that Biennial Report, within this one, as required by Section 486(d)(5) and Section 403 of the Public Health Service Act, 42 U.S.C. 283, which predate the reporting requirement established by the NIH Reform Act of 2006. Appendix G is provided in response to the mandate under SEC. 403 (a)(4)(C)(ii) of the Public Health Service Act to provide catalogs of disease registries and other data systems. Appendix H includes NIH funding levels for chronic diseases and organ systems. Appendix I 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 the National Institutes of Health (NIH) for Fiscal Years (FYs) 2010 and 2011. Thanks to the ongoing support of Congress, NIH continues the discovery of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. NIH has been the driving force behind decades of advances that have improved the health of people across the United States and around the world.

Remarkable Contributions

For 125 years, NIH has been at the forefront of medical research, directing critical funding to research institutions in cities, regions, and states throughout the nation and the world and stimulating lifesaving research breakthroughs. Begun as a one-room Laboratory of Hygiene in 1887, NIH today has grown into a complex and multidisciplinary engine for discovery and innovation, comprising 27 different Institutes and Centers (ICs).

NIH research advances have prompted a revolution in the diagnosis, treatment, and prevention of disease. Thanks to discoveries funded through NIH appropriations, NIH-supported research has met some of our Nation's biggest health challenges. U.S. life expectancy has increased dramatically over the past century and continues to improve, gaining about one year of longevity every six years since 1990. A baby born today can look forward to an average life span of over 78 years, almost three decades longer than a baby born in 1900.[1]

We have made impressive gains against cardiovascular disease. In the mid-20th century, cardiovascular disease caused half of U.S. deaths, claiming the lives of many people still in their 50s or 60s.[2] Between 1968 and 2008, deaths due to both coronary heart disease and stroke decreased by approximately 75 percent,[3] and these mortality rates continue to decline.[4] NIH-supported research led to minimally invasive techniques to prevent heart attacks and to highly effective drugs to lower cholesterol, control high blood pressure, and break up artery-clogging blood clots. NIH-funded interventions have also 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. The Centers for Disease Control and Prevention (CDC) reports that the

[1] National Vital Statistics Reports, Volume 61, Number 6 October 10, 2012. Deaths: Preliminary Data for 2011. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf.
[2] Fox, CS, et al. *Circulation.* 2004;110(5)522–7. PMID: 15262842.
[3] NHLBI Morbidity and Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases, page 26.
[4] National Vital Statistic Reports, Volume 61,Number 4 October 10, 2012. Deaths: Preliminary Data for 2011.

age-adjusted risk of death decreased by over 60 percent from 1935 to 2011, and heart disease and cancer, which accounted for 60 percent of all deaths at their peak in 1983, have dropped to 47 percent in 2011.[5]

Many chronic conditions begin as part of the aging process. One such disease, osteoporosis, can result in life-threatening bone fractures among older people. NIH-funded research has led to new medications and management strategies for osteoporosis that have reduced the hospitalization rate for hip fractures by 16 percent since 1993.[6] Science has also transformed the outlook for people with age-related macular degeneration, a major cause of vision loss among the elderly. Twenty years ago, we could do little to prevent or treat this disorder. Today, because of new treatments and procedures based in part on NIH research, 1.3 million Americans at risk for severe vision loss over the next five years now can receive potentially sight-saving therapies.[7]

Biomedical research also has benefitted those at the beginning of life. NIH-funded research has given hearing to thousands of children who were born profoundly deaf. Their hearing is made possible with a cochlear implant, an electronic device that mimics the function of cells in the inner ear. The U.S. Food and Drug Administration (FDA) approved cochlear implants for pediatric use in 2000. According to the FDA (as of December 2010), more than 28,400 children in the U.S. have received the devices, enabling many to develop normal language skills and succeed in mainstream classrooms.[8]

One of NIH's greatest achievements over the past 30 years has been to lead the global research effort against the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) pandemic. Building discovery upon discovery, researchers first achieved fundamental insights about how HIV works, and then went on to develop rapid HIV tests, identify a new class of HIV-fighting drugs, and, ultimately, figure out how to combine those drugs in life-saving ways. A recent study estimated that 14.4 million life-years have been gained among adults around the world since 1995 as a result of AIDS therapies developed through NIH funded research.[9] In addition to encouraging progress on an HIV vaccine, NIH has also led groundbreaking research on using HIV therapies to prevent new infections in uninfected individuals at high risk of infection, such that we can now envision an AIDS-Free Generation.

An Economic Engine

NIH has propelled research advances for the last 60 years by supporting a robust academic community that generates biomedical knowledge, patentable inventions, and trained scientists, including over 130 NIH-funded Nobel Laureates. NIH funding supports research personnel at more than 2,600 institutions that are located in all 50 states, the territories, and more than 90 countries around the world.

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[5] National Vital Statistics Reports, Voume 61, Number 6, October 10, 2012. Deaths: Preliminary Data for 2011. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf.
[6] *MMWR*. 2006;55(45);1221–4. PMID: 17108890.
[7] Bressler, NM, et al. *Arch Ophthalmol.* 2003;121(11):1621–4. PMID: 14609922.
[8] Francis HW, et al. *Arch Otolaryngol Head Neck Surg.* 1999;125(5):499–505. PMID: 10326806.
[9] Mahy M, et al. *Sex Transm Infect*. 2010;86(Suppl 2):ii67–71. PMID: 21106515.

Investing in NIH not only improves America's health and strengthens our nation's biomedical research potential, it propels the U.S. economy. According to United for Medical Research's report "An Economic Engine: NIH Research, Employment, and the Future of the Medical Innovation Sector," the $23.7 billion NIH spent extramurally in the U.S. in 2011 directly and indirectly supported 432,092 jobs, enabling 16 states to experience job growth of 10,000 jobs or more, propelling $62.135 billion in new economic activity.[10]

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

Unprecedented Opportunities

This is an extraordinarily exciting time to be at NIH as we witness a rapidly accelerating understanding of basic biological mechanisms that will lead to revolutionary new approaches to treat and prevent disease. This understanding is due in large part to technological advances that are changing our approach to science. In the past, most basic science projects in biomedicine required investigators to limit the scope of their studies to some single aspect of cell biology or physiology. The revolution now sweeping the field is the ability to be comprehensive: to define all the genes of a single human, or rapidly uncover all the human proteins and their structures. We need look no further than the cost of deoxyribonucleic acid (DNA) sequencing to see this dynamic at work. The cost curve for sequencing is dropping at a breathtaking rate; sequencing speed has increased even faster than computer processing speed. What's more, the average fully loaded cost of sequencing an entire genome has fallen from about $61 million a decade ago, to $7 million five years ago, to about $6,500 today. Lower sequencing costs will likely revolutionize how clinicians diagnose and treat diseases and enable the research community to pursue previously unimaginable scientific questions.

NIH is the leading supporter of basic biomedical research in the world. Our investments in basic biomedical and behavioral research make it possible to more accurately characterize 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 inestimable rewards and benefits to public health. Fostering a broad basic research portfolio is a critical component of fulfilling the NIH mission, and with the pace of discovery brought about by technological advances, we can anticipate an era of ever-expanding understanding of the fundamental mechanisms of life.

[10] Ehrlich E (2011). An Economic Engine: NIH Research, Employment and the Future of the Medical Innovation Sector, *United for Medical Research*. Available at: http://www.eyeresearch.org/pdf/UMR_Economic%20Engine_042711a.pdf.

Just as important to our mission is the translation of basic biological discoveries into clinical applications that can benefit all. Translational research is a complex process that involves a series of intricate steps. These steps range from the discovery of basic information about the causes of disease; an assessment of whether that information has the potential to lead to a clinical advance; the development and optimization of therapeutics to test in human trials; and, ultimately, the application of the approved therapy, device, or diagnostic in the real world. Drugs exist for only about 250 of the more than 4,400 conditions with defined molecular causes. And it takes far too long and far too much money to get a new drug into our medicine cabinets. This is an old problem that cries out for new and creative solutions.

In the past, drug development was based on a short list of a few hundred targets, but with advances in technology, we are now able to identify thousands of new potential drug targets.[11] We can also study whole pathways, organ systems, or even entire organisms rather than limiting the research to a single aspect of cell biology or physiology. Technologies such as large-scale sequencing, robotic high-throughput screening, and real-time imaging modalities uncover massive amounts of data that may one day lead to new therapies to prevent, treat, and cure diseases.

But this is not the only way in which technology contributes to this potential revolution in health care. Development of innovative point-of-care technologies is bringing diagnostics and therapeutics to patients' bedsides while reducing costs.

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. Chronic burdens placed on our healthcare system through conditions such as obesity, mental disorders, and Alzheimer's disease demand the innovative, scientifically-based solutions that NIH research derives. In addition to these highly prevalent conditions, there are more than 6,800 rare diseases that affect an estimated 25 to 30 million Americans. NIH is often the only hope for those suffering from these neglected diseases.

We have never witnessed a time of greater promise for advances in medicine than right now. Recent technological advancements have made the current pace of discovery unimaginable only a few years ago. We need to capitalize on this moment and tackle the maladies that afflict millions of Americans and people around the world. And we need to continue to improve our nation's health. We have achieved much since NIH's beginning as a one-room laboratory, but we face many scientific challenges ahead. If our nation can exploit today's unprecedented opportunities in biomedical research across the spectrum from basic science to clinical application, we will be amazed at what tomorrow brings.

—Francis S. Collins, M.D., Ph.D.

[11] Collins FS. *Sci Transl Med.* 2011;3(90):90cm17. PMID: 21734173.

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 the burdens of illness and disability.

The Goals of the Agency Are:

- to foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health;
- 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; and
- 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;
- the understanding of mental, addictive, and physical disorders; and
- directing programs for the collection, dissemination, and exchange of information in medicine and health, including the development and support of medical libraries and the training of medical librarians and other health information specialists.

Overview of NIH Structure and Organization

NIH is the primary federal agency for leading, conducting, and supporting biomedical and behavioral research. Composed of the Office of the Director and 27 Institutes and Centers, NIH employs approximately 18,000 people and is the steward of a $30 billion budget (FY 2011). The leadership and financial support NIH provides to biomedical, behavioral, and social science researchers extends throughout our nation and the world.

Institutes and Centers. The 27 NIH ICs are organized with a focus on and expertise in a specific disease (e.g., cancer, diabetes), an organ system (e.g., heart, eye), life stage (e.g., children, the aging population), an overarching field of science (e.g., human genome, nursing, environmental health), or a 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 (OD). The OD is composed of several offices that provide expert advice to the NIH Director and his leadership team. It coordinates policy across the NIH research community and administers centralized support services essential to the NIH mission.

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 Laboratory Animal Welfare, Office of Policy for Extramural Research Administration, Office of Extramural Programs, Office of Research Information Systems, Office of Planning and Communication, and Office of Administrative Operations.

The Office of Intramural Research (OIR) is responsible for oversight and coordination of intramural research conducted within NIH laboratories and clinics. Offices within OIR include the Office of Intramural Training and Education, Office of Technology Transfer, Office of Human Subjects Research, and the Office of Animal Care and Use.

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. In addition, DPCPSI manages the NIH Demonstration Projects in High Risk/High Reward Research, an initiative to test new ways of fostering innovation, which was also authorized through the Reform Act. Lastly, DPCPSI plans, supports, and provides technical assistance for NIH program evaluations and manages NIH planning and reporting that are required by the Government Performance and Results Act and other government-wide performance assessment activities. The program offices within DPCPSI are the Office of Strategic Coordination, which manages the NIH Common Fund, the Office of AIDS Research (OAR), the Office of Behavioral and Social Sciences Research (OBSSR),

the Office of Disease Prevention (ODP), and the Office of Research on Women's Health (ORWH), and the Office of Research Infrastructure Programs (ORIP).[12]

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

NIH Common Fund programs are intended to be:

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

DPCPSI also manages four OD program offices—OAR, OBSSR, ODP, and ORWH. The Office of Dietary Supplements is a component within 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.

The 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.

Other OD offices that advise the NIH Director, develop NIH policy, and provide essential NIH-wide oversight and coordination include the Office of Communications and Public Liaison, the Office of Science Policy, the Office of Legislative Policy and Analysis, the Office of Management, the Office of Equal Opportunity and Diversity Management, the NIH Ethics Office, and the Office of the Chief Information Officer.

[12] 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 (ORIP), DPCPSI, OD, NIH. ORIP directly funds research through a separate award authority from those used by ICs.

ICs and OD offices. The following is a list of NIH ICs and select OD program offices presented in the order in which they appear on the appropriation table in the Congressional Justification. Appendix B provides brief descriptions of the missions of the ICs and OD program offices and links to their strategic plans. The mission statements and strategic plans provided in Appendix B classify and justify NIH priorities. Historical information about NIH, including the establishment of the categorical Institutes, Centers, and specialized offices, is maintained by the NIH Office of History, a component of 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)
- 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 Research Resources (NCRR)[13]
- National Center for Complementary and Alternative Medicine (NCCAM)
- John E. Fogarty International Center (FIC)
- National Library of Medicine (NLM)

[13] 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).

- 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 (DPCPSI)
- Office of Extramural Research (OER)
- Office of Intramural Research (OIR)
- 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

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.

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 2,600 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 abroad. In FY 2011, NIH funded more than 35,000 principal investigators through research grants, with many thousands more personnel supported by the projects. With NIH support, these investigators, with 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 primary 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 close out of awards. eRA also provides services to other operating divisions of the Department of Health and Human Services (HHS), as well as other federal agencies, and supports more than 100,000 investigators worldwide.

Grants Overview

NIH announces the availability of funds for grant programs by issuing funding opportunity announcements (FOAs)[14] in the *NIH Guide for Grants and Contracts*[15] and on http://Grants.gov. The majority of 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 the amount of administrative detail, and directs applicants to the most up-to-date source of information.

[14] 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.
[15] For more information, see http://grants.nih.gov/grants/guide/.

The main types of grant funding provided by NIH are Research Grants (R series), Career Development Awards (K series), Research Training and Fellowships (T and F series), and Program Projects/Centers Grants (P series). Activity codes that incorporate the funding series differentiate the wide variety of research and research-related awards made by NIH. 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. Receipt of an R01 traditionally is the mark of a scientist achieving scientific independence, and a faculty member's track record with R01 awards often is a significant factor in university promotion and tenure decisions. Examples of other activity codes are:

- R41/R42 and the R43/R44 for the Small Business Technology Transfer program and the Small Business Innovation Research program, respectively;
- R21 for exploratory/developmental research projects;
- R15 for Academic Research Enhancement Awards that support small-scale research projects at educational institutions that have not been major recipients of NIH research grants;
- R24 for research projects that will enhance the capability of biomedical research resources;
- R25 for research education projects;
- F32 for postdoctoral individual fellowships under the National Research Service Award;
- T32 for enabling institutions to make several National Research Service Awards for both pre- 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, which have a specific major objective or a basic theme; and
- P30 for shared resources and facilities at research centers.

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

Other funding mechanisms are often applied to more unique applications. 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 research conducted by the Superfund Research Program is funded and administered by the NIEHS in coordination with the U.S. Environmental Protection Agency (EPA), 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. A research contract is typically used 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, non-profit organizations, and profit making organizations. Contract opportunities are announced in the *NIH Guide for Grants and Contracts* and also on the federal-wide Web site 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 (the first tier of peer review) and are most programmatically relevant and therefore should be considered for funding (the second tier of peer review). The NIH peer review process is designed to be fair, equitable, timely, and free of bias. The NIH 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).[16]

The Center for Scientific Review 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 that has a mission encompassing the aims and objectives of the application and potential interest 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 initiative. 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 non-federal experts qualified by training or experience in particular scientific or technical fields, or as authorities knowledgeable in the various disciplines and fields related to the applications under review. No more than one-fourth of the members of any SRG may be federal employees. SRGs may also include public members with perspective on the public health impact of the research being considered.

[16] For more information, see http://grants.nih.gov/grants/peer_review_process.htm.

The second level of peer review is performed by the National Advisory Councils of each IC, which are composed of scientific and public members chosen for their expertise, interest, or activity in matters related to a specific area of science, health, and/or disease. The vast majority of SRG -reviewed applications assigned to an IC go to the respective Council,[17] 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 favorably 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, requirements specified in congressional appropriations, programmatic relevance, IC priorities, and availability of funds.

Many ICs establish a "payline," which is a percentile-based[18] 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 expected by NIH and the IC to be available for such projects. Applications that score within the payline are most likely to be funded. However, Advisory Councils consider, evaluate, and make recommendations on specific applications that score both within and beyond the payline.

In addition to setting paylines, many ICs establish procedures for funding applications that scored beyond the payline. 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.

Prior to 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 necessary and appropriate policies in place for avoidance of financial conflicts of interest in research.

[17] 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.

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

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 to ensure responsible conduct of research. Scientific monitoring includes reviewing yearly progress and financial reports submitted by grantees, the publications generated by the research, and any invention reports.[19] NIH also monitors compliance with federal laws and policies pertaining to protection of human subjects, the care and use of vertebrate animals used in research, data sharing, the NIH Public Access Policy, and other matters. In addition, oversight of clinical research may involve data and safety monitoring and monitoring of inclusion of participants by sex/gender, race, and ethnicity in clinical research.

Intramural Research Program

Approximately 11 percent of NIH funds support research and training activities carried out by NIH scientists in NIH laboratories on its campuses in the Bethesda (including the NIH Clinical Center), Rockville, Frederick, and Baltimore areas in Maryland; Research Triangle Park, North Carolina; Detroit, Michigan; Phoenix, Arizona; and the Rocky Mountain Laboratories in Hamilton, Montana. Approximately 1,200 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. OIR is led by the NIH Deputy Director for Intramural Research, and each IC intramural research program is led by an IC Scientific Director. OIR oversight is carried out in conjunction with the IC Scientific Directors. A summary of policies governing intramural research can be found in the *Intramural Research Sourcebook*.[20]

The NIH intramural research programs conduct basic, translational, and clinical research. Organizationally, the individual laboratories and clinics report to their respective IC and are responsible for conducting original research consistent with the goals of the IC. Most ICs have an intramural program. As with the extramural program, intramural research proposals are generated by scientists. In the intramural research program, however, program directions and research priorities are not shaped primarily through grant awards[21] but rather through professional hiring and promotion decisions, external reviews, and the allocation of resources to laboratories and branches.

Each intramural research program 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

[19] For more information, see http://grants.nih.gov/grants/funding/sbir_sttr_invention_letter.htm, http://grants.nih.gov/grants/guide/notice-files/not95-003.html, and https://s-edison.info.nih.gov/iEdison/timeline.jsp.
[20] For more information, see http://sourcebook.od.nih.gov/.
[21] The exception is that intramural investigators are eligible to compete for most NIH Roadmap initiatives to allow qualified intramural researchers to contribute to the goals of Roadmap programs.

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

Two offices manage research training for OIR. The Office of Intramural Training and Education is charged with helping trainees in the intramural research program, including graduate students in partnership with universities in the U.S. and abroad, to develop scientific and professional skills needed to become leaders in the biomedical research community. The Office of Clinical Research Training and Medical Education deals with all aspects of clinical training.

NIH also provides primary administrative and research capacity for the National Toxicology Program, a federal interagency research program headquartered at the NIEHS, whose goal is to safeguard the public by identifying which of the many thousands of chemicals and other substances that humans are exposed to in the environment are toxic and may affect human health. Current National Toxicology Program initiatives examine the effects of cell phone radiation, endocrine disruptors, and nanomaterials, as well as developing new approaches to advance high throughput (high speed and high quantity) screening of chemicals, and to reduce the number of animals used in research.

NIH Clinical Center

The Clinical Center is the nation's largest hospital devoted entirely to clinical research and patient care. Research at the Clinical Center is conducted with access to cutting-edge technologies in an environment of compassionate care. This world-class national resource promotes translational research—the transformation of scientific observations and laboratory discoveries into applications for diagnosing, treating, and preventing disease that benefit patient health and medical care. Composed of two facilities—the Mark O. Hatfield Clinical Research Center (2005) and the original Warren Grant Magnuson Clinical Center (1953)—the center houses 240 inpatient beds, 82 day-hospital stations, an ambulatory care research facility, 12 operating rooms, critical care facilities, advanced radiology and imaging capabilities, and research laboratories. The unique design of the facility locates patient care units in proximity to laboratories conducting related research. This design facilitates interaction and collaboration among intramural clinicians and researchers to enhance patient care.

More than 1,500 studies are in progress at the Clinical Center, bringing 10,000 new research participants per year from all 50 states and throughout the world. The center has more than 95,000 outpatient visits a year and 6,000 inpatient admissions. Approximately 1,200 credentialed physicians, dentists, and Ph.D. researchers, 620 nurses, and 450 allied health care professionals, such as pharmacists, dietitians, and medical technologists, work at the center. As a research facility, the Clinical Center enrolls healthy volunteers and patients with common and rare conditions. Those with mysterious conditions that have

long eluded diagnosis are also seen through the Undiagnosed Diseases Program, a clinical research program in collaboration with the NIH Office of Rare Diseases and NHGRI.

In 2011, the Clinical Center received the Albert and Mary Lasker Foundation's Lasker~Bloomberg Public Service Award, "for serving since its inception as a model research hospital—providing innovative therapy and high-quality patient care, treating rare and severe diseases, and producing outstanding physician-scientists whose collective work has set a standard of excellence in biomedical research."

In addition to the Clinical Center 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, as well as identifying populations at increased risk, with the goal of developing novel preventive and therapeutic strategies to address human disease.

Providing the Platform for Discovery

Research Training and Career Development

The biomedical and behavioral research conducted and supported by NIH—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 meet the demands of emerging problems in medicine and health and 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 that trainees and newly trained investigators will not only be exposed to the latest research findings and techniques, but also that they will be positioned to respond to developing national and international public health needs. NIH takes extra efforts to foster new investigators that 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 pre-doctoral 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 regularly scheduled analyses of the research workforce. Chief among these assessments are recurring studies conducted by the National Academy of Sciences, which provide guidance on the fields in which researchers are likely to be required, as well as on the number of new investigators needed in the biomedical, behavioral, and clinical sciences. NIH also routinely evaluates the outcomes of its training programs, comparing the subsequent research involvement of students and postdoctoral scholars who participate in NIH research training with 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 in its extramural and intramural research communities, through institutional training awards and 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.

Catalogs of Research Training Activities

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

- Funded Ruth L. Kirschstein National Research Service Award (NRSA) and NLM *Institutional* Research Training Grants, FY 2009 and FY 2010
- Funded Kirschstein-NRSA *Individual* Fellowship Awards, FY 2010 and FY 2011

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 and 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 National Research Service Award[22] (NRSA) program. The goal of the NRSA program 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 always includes instruction in the responsible conduct of research. All ICs with funding authority award NRSA institutional research training grants and fellowships, 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 over 16,000 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every state in FY 2011. Institutional training grants form the core of NIH's

[22] For more information, see http://www.nigms.nih.gov/Training/RuthKirschstein.

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 on 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, have the option of applying directly to NIH for an individual research training fellowship. 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 and retain trainees from underrepresented groups, including racial and ethnic groups and individuals with disabilities. Through the Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship (F31) to Promote Diversity in Health-Related Research,[23] NIH also provides graduate students from underrepresented groups with opportunities to pursue research training through individual fellowship awards. Because part of the inherent challenge of recruiting talented individuals into research training programs is to have a pool of prepared applicants from which to draw, NIH offers undergraduate research training to honors students who have an explicit interest 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 at selected institutions.

The relative diversity of research training participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Among FY 2011 trainees and fellows who reported their race and ethnicity, 66 percent were White, 15.3 percent were Asian, 7.7 percent were African American, 8.6 percent were Hispanic, 1 percent were Native American, and 0.6 percent were Native Hawaiian or Pacific Islanders. More than 52 percent of trainees and fellows in FY 2011 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[24] (CTSAs) administered by NCRR.[25] Now active at 60 sites around the

[23] For more information, see http://grants1.nih.gov/grants/guide/pa-files/PA-11-112.html.
[24] For more information, see http://www.ncats.nih.gov/research/cts/ctsa/ctsa.html.

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 over 900 NRSA trainees and new investigators annually. (CTSA trainees are included in the NRSA data provided in Appendix E.) NCRR also joined forces with NCI, NIDA, NIGMS, and NINR to provide career development opportunities for young investigators interested in cross-training in patient-oriented research, pharmacogenomics, and personalized medicine.

Another trans-NIH initiative is the Early Independence Awards.[26] These awards, supported by the NIH Common Fund, provide newly-trained scientists who are ready and able to work independent of a mentor a chance to forgo the traditional period of postdoctoral training after receiving their doctoral degree and pursue their own program of independent research. The first group of 10 such new investigators to receive these awards was selected in 2011 and is being closely monitored to determine the effects of early research funding on innovation.

In addition to its formal research training programs, NIH supports graduate and postdoctoral research experiences on research grants. Though not an NIH "program" per se, the impact of this support 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 provide a better understanding of how graduate students and postdoctorate fellows contribute to research projects, NIH investigators were asked to identify all research project personnel on their annual progress reports, beginning with those due in FY 2010. After analyzing the first full year of data, NIH has calculated that more than 23,000 graduate students and 28,000 postdoctorate fellows are employed as research assistants or associates on research grants. As these personnel data continue to accrue, NIH plans further analyses to obtain a greater understanding of the staffing patterns of research grants and the biomedical research workforce supported by its funding.

IC Programs and Initiatives

Because each NIH IC has its own particular research mission, individual ICs are responsible for determining how the workforce needs identified by the National Academy of Sciences and others 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, a number of ICs also make

[25] On December 23, 2011, President Barack Obama signed the Consolidated Appropriations Act, 2012 (P.L. 112-74). As part of this legislation, the National Center for Research Resources (NCRR) is dissolved and the National Center for Advancing Translational Sciences (NCATS) is established. Science Education Partnership Awards (SEPA) is now part of the NIH Office of the Director, Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs.

[26] For more information, see http://commonfund.nih.gov/earlyindependence/.

awards for M.D./Ph.D. and other types of dual-degree training. The oldest and largest of these is the NIGMS Medical Scientist Training Program, which supports exceptional students pursuing an integrated program of graduate training in the biomedical sciences and clinical medicine.

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 a number of selected programs provide opportunities to U.S. students and postdoctoral fellows interested in global health research. Ultimately, the aim of FIC's research training programs is to strengthen sustainable research capacity in the developing world.

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 grants[27] (T15s), which 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 or dental informatics. NLM also offers a clinical informatics research 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.

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[28] (K awards) 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[29] accelerates the transition from mentored to independent research by providing a bridging mechanism of an initial mentored period of 1–2 years followed by an independent phase, during which awardees establish their own research programs and apply for independent research support. Other "mentored" career development awards provide support for a sustained period of "protected time" for intensive research career

[27] For more information, see http://www.nlm.nih.gov/ep/GrantTrainInstitute.html.
[28] For more information, see http://grants.nih.gov/training/careerdevelopmentawards.htm.
[29] For more information, see http://grants1.nih.gov/grants/guide/pa-files/PA-11-197.html.

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 regularly reviewed and evaluated. The National Academy of Sciences has undertaken regular reviews of the medical research workforce and made recommendations for modifications in the size and focus of the NRSA program. In addition, NRSA program processes and outcomes are regularly assessed through recurring program evaluations and performance is evaluated annually using Government Performance and Results Act (GPRA) goals. These reviews have been coordinated by OER, which oversees the NRSA program.

NAS reviews. Over the past 30 years, the NRSA program has been the subject of more than a dozen studies by the National Academy of Sciences, 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. The most recent National Academy of Sciences report on research training, published in 2011, noted that the NRSA program has "set the standard" for research training.[30]

The recurring nature of these National Academy of Sciences studies ensures that NIH research training programs reflect changes in science and research needs that inevitably occur over time. In recent years, NIH has followed recommendations from National Academy of Sciences committees for enhancing stipend levels, promoting the early completion of research training, and improving workforce data collection and analysis.

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 faster, are more likely to pursue research careers, and have greater subsequent success in research than do students not participating in NRSA programs.[31] Similarly, assessments of NRSA postdoctoral training have found that NRSA postdoctoral fellows are more likely to successfully pursue research careers. In FY 2011, around 30 percent of former NRSA postdoctoral fellows who subsequently applied for a major NIH research grant received funding, compared to 17 percent of other postdoctoral fellows.[32]

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,

[30] For more information, see http://grants.nih.gov/training/Research_Training_Biomedical.pdf.
[31] For more information, see http://grants.nih.gov/training/career_progress/index.htm.
[32] For more information, see http://www.hhs.gov/budget/performance-appendix-fy2013.pdf.

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.[33] While all investigators receiving these career development awards fared well, the opportunity for 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 three GPRA measures. In the first two measures, NIH seeks to assess the quality of its programs and determine if 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 successfully receive NIH research grant support against their peers. Subsequent NIH support is one of several measures that reflect the impact of NRSA research training on participants' ability to successfully pursue and sustain a research career. To date, NIH has generally met these GPRA measures because NRSA trainees and fellows consistently outperform their counterparts.

The third training-related GPRA measure assesses NIH progress in improving the efficiency of NRSA program management by developing and implementing the xTrain electronic system for appointing trainees to institutional training grants. The system was piloted in 2008, improved, and then required NIH-wide in mid-2011. By the end of FY 2011, 99.3 percent of trainee appointment forms were submitted electronically. In 2012, when the system is fully implemented, xTrain is expected to save substantial staff time and eliminate data entry errors while increasing NIH's efficiency and enhancing the integrity of data used for program monitoring and evaluation purposes.

Institute and Center training evaluations. In addition to scheduled NIH-wide assessments of programs coordinated through OER, individual NIH ICs undertake periodic, targeted evaluations to improve implementation and assess outcomes of their own training programs. For example, as mandated by the NIH Reform Act of 2006 (Pub. L. No. 109-482), in 2010-2011, NCRR conducted an evaluation of the outcomes and effectiveness of CTSA training programs. The evaluation[34] included surveys of trainees, scholars, and mentors and addressed pediatric clinical research training issues in particular.

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 of the programs; 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

[33] For more information, see http://grants.nih.gov/training/K_Awards_Evaluation_FinalReport_20110901.pdf.
[34] For more information, see https://www.ctsacentral.org/sites/default/files/files/CTSANationalEval_FinalReport_20120416.pdf.

coordinate activities pertinent to the review, administration, management, and evaluation of training grants and fellowships.

Intramural Activities

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

Among the intramural program's offerings are summer internships for high school, college, and graduate students. Recent college graduates who plan to apply to graduate or professional school also can spend a year engaged in biomedical research working side by side with NIH scientists. Current graduate students can spend a summer, or a year, as fellows engaged in biomedical research at NIH. The Graduate Partnerships Program[35] enables students to pursue research at NIH toward their degrees 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 Clinical Research Training Program[36] provides research-oriented medical and dental students an opportunity to engage in a mentored clinical or translational research project on the NIH campus.

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[37] provides the opportunity for 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. For clinicians, there are 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 intramural program increasingly has focused on helping graduate students and postdoctoral fellows develop their career skills. To ensure that intramural trainees and fellows can successfully advance in their careers, NIH offers courses in scientific writing and grant writing, as well as presentation and teaching skills. In addition, intramural trainees and fellows—indeed, all members of the NIH community—benefit from access to a wealth of NIH courses, seminars, and science career resources.

[35] For more information, see https://www.training.nih.gov/programs/gpp.
[36] For more information, see http://www.cc.nih.gov/training/crtp/crtp.html.
[37] For more information, see https://www.training.nih.gov/programs/postdoc_irp.

In late 2011, NIH unveiled plans for a new "intramural-extramural" partnership to nurture the next generation of clinical researchers, funded in part by the Lasker Foundation. Individuals selected as Lasker Clinical Research Scholars[38] have the opportunity to serve as an investigator in the NIH intramural program. If they choose to work in an extramural setting after their time as a Lasker Scholar, they can qualify for additional years of support at an extramural research institution.

NIH Loan Repayment Programs

The NIH Loan Repayment Program[39] is 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 Program provides financial assistance for educational debt in exchange for a two- or three-year research commitment. Over 1,600 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, or as an NIH employee.

Science Education and Literacy

To remain a world leader in biomedical research we must encourage and support students' curiosity and interest in science throughout their education. NIH funds a number of science education and literacy activities from grammar school to undergraduate students. These programs support curriculum development, mentoring programs, 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 the science knowledge and skills of students, attract young people to biomedical and behavioral science careers, lay the groundwork for advanced study, enhance public understanding of health science, and empower the public as consumers of science and health information.

Curriculum supplements—ready-to-use, interactive teaching units—are one of NIH's most popular and effective science education efforts. Crafted through a unique collaboration of NIH scientists, teachers, and expert curriculum developers, the supplements are aligned with state education standards and are consistent with the National Science Education Standards. NIH has shipped more than 430,000 curriculum supplements upon request to K-12 educators across the nation. Topics covered include *The Science of Healthy Behaviors*, *Cell Biology and Cancer*, *The Brain: Understanding Neurobiology through*

[38] For more information, see http://www.nih.gov/science/laskerscholar/ or http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-12-001.html.
[39] For more information, see http://www.lrp.nih.gov/index.aspx.

the Study of Addiction, and *Exploring Bioethics*. The newest additions are *Evolution and Medicine* for high school biology classes and *Rare Diseases and Scientific Inquiry* for middle schools.[40]

NIH's *Diabetes Education in Tribal Schools Project*[41] is a K-12 curriculum developed to increase the understanding of health, diabetes, and maintaining life in balance among American Indian/Alaska Native students; increase American Indian/Alaska Native students' understanding and application of scientific and community knowledge; and increase interest in science and health professions among American Indian/Alaska Native youth. The project aims to change perceptions, knowledge, and attitudes about diabetes through classroom learning experiences that will empower students to adopt healthier lifestyles.

NIH provides other types of school resources as well. *Findings*[42] is a semi-annual 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. A companion Web site offers videos, podcasts, and interactive games expanding on the printed material. NIH also offers topical publications and school resources, such as slide kits, online quizzes, and science puzzles that are used by teachers across the country to augment textbooks and enrich the classroom experience. Subject areas include cell biology, genetics, structural biology, chemistry, pharmacology, and computational biology. Classroom posters linked to selected publications also promote interest in science and research careers and continue to be tremendously popular.

NIH aims to engage students and the public in the wonders of biology and biomedical research through other programs, as well. For those who are interested in a career in the life sciences, NIH provides resources such as LifeWorks®, a career exploration Web site for middle and high school students, and their parents, teachers, and career guidance counselors.[43] Users can search the site for in-depth information on more than 125 health and medical science-related careers and generate a customized list of careers that match their skills and interests. SciLife is an annual health and biomedical career-planning workshop for parents and high school students.[44] NIH also sponsors a speakers' bureau that provides engaging science professionals to talk to school groups and local and national organizations.

The NIH Blueprint for Neuroscience Research, a cooperative effort among 16 NIH Institutes, Centers and Offices that support neuroscience research, offers 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 as well as inspire future generations of neuroscientists. The grants focus on providing innovative neuroscience education to children throughout the U.S. through a variety of mechanisms, such as the development of interactive teaching modules that can be accessed on iOS devices (e.g., the

[40] These curriculum supplements are free to teachers and may be ordered at http://science.education.nih.gov/supplements.
[41] For more information, see http://www3.niddk.nih.gov/fund/other/dets/index.htm.
[42] For more information, see http://publications.nigms.nih.gov/findings.
[43] For more information, see http://science.education.nih.gov/LifeWorks.
[44] For more information, see http://science.education.nih.gov/SciLife.

iPad), innovative Web-based games for classroom use, and museum exhibits that include interactive components as well as classroom activities.

NCRR's Science Education Partnership Award (SEPA) program[45] enables researchers, educators, and community groups to share their knowledge, expertise, and enthusiasm about health and science research with K-12 students and the general public. SEPA-funded classroom- and museum-based projects generate resources, such as hands-on and problem based curricula, interactive health exhibits, films, and after-school and summer student intern and teacher professional development opportunities. The SEPA Web site, http://www.nihsepa.org, maintained by the SEPA community, provides universal access to educational resources, teachers training, health-based museum exhibits, and evaluation models that are developed by these SEPA-funded projects.

Individual NIH ICs also have science education programs focused on their specific missions. For example, NIDA supports a Science Education in Drug Abuse Partnership Award, modeled after the SEPA program. The purpose of the Science Education in Drug Abuse Partnership Award program is to fund the development and evaluation of innovative programs and materials for enhancing knowledge and understanding of neuroscience and the biology of drug abuse and addiction among K-12 students, the general public, health care practitioners, the media, and other groups.

[45] On December 23, 2011, President Barack Obama signed the Consolidated Appropriations Act, 2012 (P.L. 112-74). As part of this legislation, the National Center for Research Resources (NCRR) is dissolved and the National Center for Advancing Translational Sciences (NCATS) is established. Science Education Partnership Awards (SEPA) is now part of the NIH Office of the Director, Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs.

Chapter 2
Overview of NIH Research

Introduction

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 the burdens of illness and disability, NIH conducts and supports biomedical and behavioral research across a broad spectrum of scientific disciplines and approaches. NIH scientists may have been trained in any number of disciplines, from molecular biology to demography to engineering. Yet, as science and technology have advanced and the complexity of the issues addressed has grown, the disciplinary boundaries that previously defined science have become blurred, such that NIH research is not delineated by scientific discipline, but instead by a continuum of inquiries.

NIH research is predicated on the understanding of ongoing and newly emerging public health needs. As these needs are identified, scientific approaches are brought to bear across a continuum of research designed to understand basic causes and mechanisms of disease, find new ways of identifying and interrupting disease processes based on this understanding, and bring these new interventions into common practice so that all may benefit. The path from basic research to clinical practice (see Figure 2-1) is not a continuum in the strictest sense, because all steps of biomedical and behavioral research, from basic to translational to clinical, can inform other areas. For example, findings in clinical research can provide new areas of inquiry in basic science.

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

Step 1. 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.

In the past, most basic science projects in biomedicine required investigators to limit the scope of their studies to a single aspect of cell biology or physiology. With the advent of technologies that can

automate research techniques at rapid speed (e.g., high throughput technology), the revolution now sweeping the field is the ability to be comprehensive (i.e., the genes of the human or a model organism, the human proteins and their structures, the common variations in the genome, the major pathways for signal transduction in the cell, the patterns of gene expression in the brain, the steps involved in early development, and the components of the immune system). Technologies contributing to these advances, many of which have moved from the development stage to broad use across the research community in the last few years, include DNA sequencing, microarray technology, nanotechnology, new imaging modalities, and computational biology.

Step 2. 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 *early (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 often are 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.

This is an extraordinarily exciting time to advance translational science and speed the development of new cures. Through the application of genomic research and high throughput technologies, breakthroughs in understanding of the causes of many diseases and the identification of 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 development of new diagnostics and treatments for a wide range of diseases, opening a door of opportunity in translational science.

Step 3. Medical advances arise from rigorous testing of new strategies for recognizing and intervening on disease processes, whether intervention occurs before it manifests (prevention) or after it takes hold (treatment). *Clinical research* is patient-oriented research that is conducted with human subjects (studies that involve 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, and the testing and refinement of new technologies.

Clinical trials, a crucial subset of clinical research, provide the best method to determine whether diagnostics and interventions are safe and effective in people and to assess side effects or other complications. There are many different types of trials that are designed to answer specific research questions about a biomedical or behavioral intervention. For example, treatment trials might test experimental drugs or devices, new combinations of drugs, innovative approaches to surgery or radiation therapy, or behavioral interventions such as exercise training or medication adherence. Prevention trials test the effectiveness of approaches to prevent diseases or other adverse health conditions, or to keep them from recurring. Comparative effectiveness research entails real-world comparisons of known interventions. Screening and diagnostic trials are conducted to find better ways to detect or diagnose diseases or conditions. Finally, 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.

Additionally, NIH supports clinical and translational studies unlikely to garner substantial investment by other sources because of insufficient financial incentives. For example, studies that address rare diseases are unlikely to be conducted by for-profit entities because of the small number of patients that will make use of new interventions.

Step 4. 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 *late (postclinical) translational stage* takes results from studies in humans and optimizes them to have broad applicability. For example, NIH supports research that will identify factors that enhance access to and implementation of new interventions. Studies in this area include the development and testing of novel models and methods to best implement newly discovered interventions in order to reach diverse groups and populations (e.g., racial/ethnic groups, rural populations). The focus of health services research is on optimizing the health care delivery system to reflect the latest medical advances.

Step 5. 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 terms of 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 (e.g., FDA, CDC) and outside the Department (e.g., Veteran's Administration, Department of Defense). NIH also partners with non-governmental agencies, scientific organizations, patient advocacy groups, and healthcare delivery systems. These partnerships provide the American public with a healthcare system that will enhance health, lengthen life, and reduce the burdens of illness and disability.

Step 6. 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 for use with patients, and clinical researchers make new observations about the nature and progression of disease that often produce feedback to stimulate new basic investigations. Research on new outreach approaches and the comparative effectiveness of prevention and treatment strategies not only address the feasibility of the strategies themselves, but in turn inform the development of future interventions.

In the process of translating basic research into clinical practice, NIH supports the development of research technologies, which provide innovative tools that are 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 inter-related bioinformatics platforms, NIH researchers across the spectrum are able to share technologies that were only dreamed of a few years ago.

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. In-depth understanding and monitoring of public health is therefore a vital function of the PHS. NIH works in concert with other PHS agencies (e.g., Centers for Disease Control and Prevention [CDC] to identify and monitor public health needs through its support of epidemiological studies). Epidemiological studies examine factors that contribute to health and disease in human populations using a broad range of approaches. Persons or groups can be followed over time in longitudinal studies, or a snapshot of information can be collected 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, by 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 up of individuals who share a characteristic of interest (e.g., tobacco use, age, educational status). 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.

Epidemiological research is a critical part of the activities undertaken to fulfill the NIH mission of pursuing fundamental knowledge of living systems and applying that knowledge to extend healthy life and reduce the burdens of illness and disability. Epidemiological research is important for investigating all types of disease, and 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 rumor-based surveillance as an innovative means for conducting public health surveillance.

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.

The population-based perspective provided by epidemiological 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 to factors such as high serum cholesterol levels, hypertension, and cigarette smoking. Based on these results, clinicians were able not only to identify patients at high risk for cardiovascular disease but, even more important, to develop interventions that reduce risk. More recently, a series of NIH studies revealed an increased risk of cancer following exposure to benzene at low levels and documented blood toxicity following exposure levels of under one part per million.[46,47] These data were used by the U.S. Environmental Protection Agency (EPA) as it developed a new rule in 2007 limiting the benzene content in gasoline and adopting new standards for passenger vehicles and portable fuel containers to limit emissions of benzene and other hazardous air pollutants.[48]

NIH Epidemiological Research Activities

In the area of epidemiological research, NIH often leverages its investment by working with other agencies. For example, numerous NIH Institutes collaborate with CDC to collect population-based information through CDC's many surveys. For example, NIDCD collaborated with CDC to incorporate several measures into CDC surveys to boost knowledge on the prevalence of hearing, 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.

A collaboration between the Department of Defense and NIMH, the Army Study to Assess Risk and Resilience in Service Members (Army STARRS) is the largest study of suicide and mental health among military personnel that has ever been undertaken.[49] The goal of the five-year 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 current data being collected 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. Related to this research, NIMH and the U.S. Marine Corps signed a memorandum of agreement in August 2011 to begin collaboration with researchers from the Marine Resilience Study.

Another example of an intergovernmental collaboration is the Agricultural Health Study, cosponsored by two NIH Institutes (NCI and NIEHS) and EPA.[50] 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

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[46] Hayes RB, et al. *J Natl Cancer Inst*. 1997;89(14):1065–71. PMID: 9230889.
[47] Lan Q, t al. *Science*. 2004;306(5702):1774-6. PMID: 15576619.
[48] U.S. Environmental Protection Agency. Control of hazardous air pollutants from mobile sources: final rule to reduce mobile source air toxics. EP A420-F-07-01. February 2007. Available at http://www.epa.gov/oms/regs/toxics/420f07017.htm#program.
[49] For more information, see http://www.armystarrs.org.
[50] For more information, see http://aghealth.nci.nih.gov/.

higher rates of some types of cancer and other conditions including diabetes, asthma, neurologic disease, and reproductive problems. A recent Agricultural Health Study study showed that private and commercial pesticide applicators who used the common agricultural herbicide atrazine were at increased risk of thyroid cancer.[51] Another study evaluated the interaction between gene variants which have been shown in previous studies to increase prostate cancer risk and pesticide use. Interactions with these variants were observed with the organophosphates insecticides fonofos, terbufos, coumaphos, and phorate and the pyrethroid, permethrin.[52]

Given its stable budget and long existence, NIH has been able to invest in a number of important longitudinal studies. For example, NIA supports a robust portfolio of longitudinal demographic and economic research, including studies to estimate the health and economic consequences of aging. The Health and Retirement Study (HRS) is a premier source of data on the health and socioeconomic circumstances of older Americans, including information about retirement, income, pensions and health.[53] It provides uniquely rich, nationally representative longitudinal data for the community of scientific and policy researchers who study the health, economics, demography, sociology, and psychology of aging, creating opportunities for new types of interdisciplinary research. Funds from the American Recovery and Reinvestment Act (ARRA) facilitated expansion of the study, including genotyping DNA samples from participants and doubling the minority sample to facilitate research on vulnerable populations. HRS has also become a model for an international collection of aging studies that support cross-national comparative research.

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. Childhood cancers are rare, representing less than 1 percent of all new cancer diagnoses. The Annual Report to the Nation on the Status of Cancer,[54] released by NCI, CDC, American Cancer Society, and the North American Association of Central Cancer Registries in March 2011, and reporting on a data period of 2003–2007, found for the first time that lung cancer death rates decreased in women, more than a decade after rates began dropping in men. The report was informed by the NCI SEER (Surveillance Epidemiology and End Results) Cancer Statistics review. The review was last updated in November 2011 and covers 1975–2008.

NIDDK's The Environmental Determinants of Diabetes in the Young (TEDDY) study was established to identify potential environmental factors, including 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 over 8,000 high-risk newborns and is collecting biosamples for analysis to identify potential triggers of type 1 diabetes. Children enrolled in the study are developing autoimmunity and type 1 diabetes at predicted rates, indicating that those at risk can be accurately identified, and that the study is on track to make a major contribution. Identification of an infectious agent that triggers autoimmunity could lead to a vaccine to protect against type 1 diabetes. Or, if dietary

[51] Freeman LE, et al. *Environ Health Perspect.* 2011;119(9):1253–9. PMID: 21622085.
[52] Koutros S, et al., *Cancer Res.* 2010;70(22):9224–33. PMID: 20978189.
[53] For more information, see http://hrsonline.isr.umich.edu/.
[54] For more information, see http://www.cancer.gov/newscenter/pressreleases/2011/ReportNation2011Release and http://www.oxfordjournals.org/our_journals/jnci/press_releases/kohlerdjr077.pdf.

factors are identified that protect from or contribute to the development of the disease, changes in infant feeding practices could be recommended. NIAID, NICHD, and NIEHS also participate in this study.

The National Children's Study (NCS) was mandated by Congress in the Children's Health Act of 2000. Beginning in FY 2001, NICHD, designated as the lead agency, began planning for the study in collaboration with other federal partners. In FY 2007, Congress added new funding for the study through the Office of the Director, NIH, and has appropriated funds every year since then. The NCS is a longitudinal birth cohort observational study[55] with the goal of improving the health and well-being of children and to identify antecedents of healthy adulthood by examining the effects of a broad range of environmental influences and biological factors. The NCS will produce an unprecedented amount of information about children's health and will provide a foundation for analyzing factors that contribute to growth, development, health, and disease to guide future science and policy.

The NCS Vanguard Study, a pilot study to test design and procedures aspects of the Main study, was launched in January 2009 and has already provided a rich source of data to guide the Main NCS Study. NIH announced funding opportunities in FY 2012 for continuation of the Vanguard Study and will begin recruiting the targeted 100,000 newborns who will be the subjects of the Main Study.

Initiated in 2011, the Population Assessment of Tobacco and Health (PATH) Study 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 (FSPTCA in 2009). It is a national, longitudinal cohort study that will follow an estimated 59,000 adults and youth (12 to 18 years old) to assess susceptibility to tobacco use, patterns of use, risk perceptions, and resultant health impacts. The sample will include both males and females and persons of diverse racial, ethnic, and cultural backgrounds. Data collection is currently slated to begin in fall 2013, with plans for four or more annual data collection waves. Outcomes will inform current and future regulatory options for the FDA to protect public health, including setting tobacco product standards and communicating the risks of tobacco use to the general public.

Investments in the past continue to pay off. NIH has been investing in epidemiological research for most of its history, and some of this research involves longitudinal studies that have been ongoing for decades. Data collected from these studies continue to advance our understanding of disease and health in new and exciting ways and form the foundation for extraordinary opportunities in biomedical research today.

The Framingham Heart Study 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 first 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

[55] In July 2012, the *NCS Proposed Sampling Strategy: Main Study* document was released to structure discussions about the future of the NCS's sampling design for the National Children's Study Advisory Committee: http://www.nationalchildrensstudy.gov/about/organization/advisorycommittee/Pages/Proposed%20Sampling%20Strategy%20Main%20Study%20%28July%202012%29.pdf. The NCS is proposing a multi-layered cohort approach that involves birth, prenatal, and preconception cohorts.

generations has been analyzed as part of an initiative called the SNP Health Association Resource (SHARe). 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 National Center for Biotechnology Information's (NCBI) database of Genotypes and Phenotypes (dbGaP) 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 policymakers and assess the short- and long-term effects of policies on health or health-related behaviors. For example, in 1975, 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, and follow-up is conducted every two years with a subset of individuals from each graduating class until they reach age 30. 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.[56] 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.

A comprehensive understanding of health and disease requires consideration of factors from the molecular 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 a number of studies in the U.S. and worldwide aimed at building a comprehensive understanding of health and disease, with the goal of identifying new and more effective approaches for prevention and treatment. 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.

To facilitate research on the interactions of genes and the environment, NIEHS launched EPR, in collaboration with the University of North Carolina General Clinical Research Center, to collect DNA samples from more than 16,000 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. A unique feature of the EPR is that participants were recruited from two distinct groups—apparently healthy individuals from the general population and patients from area clinics and hospitals. Individuals in the clinic/hospital group had an array of medical conditions, and their inclusion in the EPR increases the likelihood of identifying subjects with both the genetic and clinical characteristics of interest. Unlike anonymous DNA registries, researchers using EPR are able 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

[56] National Institute on Drug Abuse. Monitoring the Future National Results on Adolescent Drug use: Overview of Key Findings 2008. Available at: http://www.monitoringthefuture.org/index.html.

that can occur in genetic epidemiology studies when subjects are recruited based primarily on their observable clinical or physical traits.

CDC estimates that about 1 in 88 children has been identified with an autism spectrum disorder.[57] CDC's data indicate that ASD prevalence has increased 78 percent since 2002. Whether the cause is attributable to a change in diagnosis criteria or to genetic or environmental factors is unclear. Multiple factors are likely to be responsible for the increase in prevalence over time. Since 2006, NIEHS has supported the Childhood Autism Risks from Genetics and Environment (CHARGE) study, 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. In one recent study, scientists demonstrated an association between a mother's living near freeways and major roadways during pregnancy and near time of delivery (a surrogate for air pollution) and the risk of having a child with autism.[58]

Research has shown that factors such as genetic background, geographic location, socioeconomic status, 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. In this regard, NIH is supporting the Multi-Ethnic Study of Atherosclerosis (MESA), a multicenter epidemiological study of cardiovascular disease in 6,900 men and women from four ethnic groups—white, African American, Hispanic, and Americans of Chinese ancestry. This study, which began in 1999 and is funded through 2015, has measured and compared the value of chest computed tomography (CT), cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for predicting the development of cardiovascular disease. In one recent finding, researchers used MESA data to confirm that CT measurements of coronary calcium, previously shown to predict coronary heart disease among white populations, are effective predictors in African Americans, Hispanics, and Americans of Chinese ancestry as well.[59]

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. The

[57] Autism and Developmental Disabilities Monitoring Network (CDC). Prevalence of Autism Spectrum Disorders — Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States 2008. *MMWR*. 2012/61(SS03);1–19. PMID: 22456193.
[58] Volk H, et al. *Environ Health Perspect*. 2011; 119(6):873–877. doi:10.1289/ehp.1002835
[59] Detrano R, et al. *N Engl J Med*. 2008; 358(13):1336–45. PMID: 18367736.

collaboration allows Consortium partners to share data from 43 cohorts composed of more than 4 million people from diverse populations. Each cohort contains extensive information on known or suspected risk factors and biospecimens collected pre- and post-diagnosis. The pre-diagnostic specimens provide a valuable resource for studies of cancer etiology and early detection. Researchers can correlate changes in molecular profiles associated with the onset of different types of disease, thereby providing valuable insights into the actual mechanisms of human carcinogenesis.

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. For example, the Hispanic Community Health Study, which is sponsored by six NIH Institutes (NHLBI, NIMHD, NIDCD, NIDCR, NINDS, and NIDDK) and the NIH Office of Dietary Supplements, includes 16,000 persons of Hispanic/Latino descent 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, and cognitive impairment.[60] 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. Particular attention will be given to the role of cultural adaptation and disparities in the prevalence and development of disease. 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.

Conclusion

Epidemiological studies are fundamental to NIH's mission, in that they play a key role in identifying public health needs, and they are essential to efforts to bridge the results of basic, translational, and clinical studies to practical applications such as clinical practice and public policy. Many NIH epidemiological studies have had substantial influence on public health, with current investments likely to follow suit. This success is due to a number of factors, including investment in long-term studies, pursuit of a comprehensive view of disease, and promotion of a culture of cooperation.

[60] For more information, see http://www.cscc.unc.edu/hchs/.

Basic Research

Basic research is a major force driving progress across the biomedical and behavioral sciences and is paramount in uncovering the fundamental principles of biology, and ultimately, the key to our understanding of 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. Therefore, fostering a broad basic research portfolio is critical for the NIH mission.

Advances in Basic Research Form Building Blocks 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 this harmony at multiple levels of analysis can break down, forming the basis of disease. For example, at the molecular level, scientists are interested in understanding how biological macromolecules—proteins, nucleic acids, sugars, and lipids—carry out cellular processes. At the cellular level, researchers are focused on understanding how cells sense and respond to their environment. And at the behavioral level, researchers are focused 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 taken to arrive at an incremental advance or a groundbreaking discovery, 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. The results of such 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 the burdens of illness and disability. In fact, each new finding serves as a building block for establishing a deeper understanding of human health and disease. NIH supports general basic research, as well as basic research focused within a specific area or context.

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. Basic research using model systems and organisms has provided the foundation of knowledge about human growth and development, behavior, the maintenance of health, and development of disease. Research on bacteria, yeast, insects, worms, fish, rodents, primates, and even plants has shown that the basic operating principles are nearly the same in all living organisms. Therefore, a finding made in fruit flies or mice may shed light on a biological process in humans and 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 are often especially useful for understanding features of disease that have similar underlying molecular causes. For example, protein-clumping defects are common to several neurological 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.

In addition to supporting individual studies of model organisms, NIH supports the development of a wide range of research models, particularly marine invertebrates and lower vertebrates, and the identification and development of new and improved animal and non-animal models for the study of human 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 intricate and interconnected pathways that facilitate communication among genes, molecules, and cells. While some pathways have already been discovered, many more remain to be found. Further research also is needed to understand how these pathways 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 discovering approaches to its control. 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 chewed up 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 brain cell.

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. Much research is underway to understand how to use products developed from stem cells as therapies to treat disease.

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 (iPS) cell. iPS cells are reprogrammed from adult cells to a pluripotent state remarkably like hESC. 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 iPS cells, and NIH support of this research area is growing.

The NIH Common Fund supported the establishment of an NIH Center for Regenerative Medicine (NIH CRM) within the NIH IRP to serve as a resource for the scientific community, providing stem cells and supporting protocols and standard operating procedures used to derive, culture, and differentiate the stem cells into different cell types. The program is intended to accelerate the development of cell-based therapies for repairing or replacing tissue damaged by disease or injury. Among various potential activities, NIH CRM is helping standardize research results across different laboratories by facilitating access to a set of well-characterized stem cell control and reporter lines. In addition, the center is negotiating uniform iPS cell deposit and distribution agreements with major human cell and tissue banking facilities for NIH researchers that can be more widely adopted. The NIH CRM Director has established numerous domestic and international collaborations. In addition to these efforts, a number of intramural iPS cell pilot research projects have been funded to stimulate iPS cell research at the NIH and to help translate findings in to the clinic, in part by serving as "test cases" for newly developed standardized procedures and resources.

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 diseases. 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, and by pathogens such as HIV that destroy immune cells.

Although a great deal 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), a trans-NIH intramural initiative launched in 2008 to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI 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). This type of research is sometimes referred to as "hypothesis-limited," because investigators cast a technological net to obtain information on the entire catalog of biomolecules within a cell or tissue before they set out to prove or disprove a specific hypothesis.

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. This investment has led to an 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 genomic 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. NCBI is charged with creating automated systems for storing and analyzing knowledge about molecular biology, biochemistry, and genetics; 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.

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 (ribonucleic acid)—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.

DNA is made up of four chemical compounds called "nucleobases." Four distinct nucleobases are found in the DNA of all organisms: adenine, thymine, guanine, and cytosine—denoted by the letters A, T, G, and C respectively. These nucleobases are attached to sugar molecules and phosphate groups to form strands. Two parallel strands are entwined in the form of a double helix, held together by nucleotide pairs. Each nucleotide in one strand links to the same partner on the other strand: A pairs with T, C pairs with G—forming what is called a "base pair." The human genome consists of about 3 billion base pairs, packaged in 23 sets of chromosomes that are wrapped extremely tightly into the nucleus of virtually every cell in the body. Identifying the base pairs—and thus the letters—and the order in which they appear on any stretch of DNA is called "sequencing" that segment.

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 generated immense scientific excitement. It provided a new means of analyzing the functions of cells, tissues, and systems in the body and offered new tools for understanding the causes of disease. It laid the foundation for broad new 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 complex, 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 for 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 myriad common diseases, such as heart disease, cancer, diabetes, and asthma, but for no common disease have all the genes involved yet been identified.

Educational resources to help the public understand genomics, including multimedia presentations, are available on the NIH Web site.[61]

As a result of the overwhelming influence of the genome on human health, virtually every NIH IC now engages in genome-related research. Like many NIH ICs, NCI supports a huge array of gene-oriented projects, including Genome-Wide Association Studies (GWAS)—in effect, full-body DNA scans—that recently detected new genetic factors involved in breast, prostate, and colon cancers. The first successful application of GWAS for age-related macular degeneration (AMD) identified an entirely new molecular pathway. In 2010, an NEI-led international consortium combined data from multiple GWAS on AMD to identify many new genetic loci. Similarly, in FY 2009, NEI conducted the largest glaucoma genetics study to date and identified two new highly significant pathways involved in glaucoma. Over the past four years, NHLBI and NIGMS have sponsored a research consortium that combined both genetic and clinical data to devise a computer algorithm for setting the proper dose of the blood-thinner warfarin, commonly prescribed for heart patients and others, the physical response to which is strongly influenced by genetic factors.[62] A major clinical trial began in early 2009 to test whether that new algorithm is better than the current trial-and-error method.

NIH researchers and grant recipients also have increased the pace of sequencing other nonhuman genomes. Full sequences of nearly 200 organisms now have been completed or are underway. 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

[61] For more information, see http://www.genome.gov/10000002.
[62] International Warfarin Pharmacogenetics Consortium. *N Engl J Med*. 2009;360(8):753–64. PMID: 19228618.

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.

Genes themselves, the "coding regions" of DNA that direct cells to make particular proteins, account for only about 2 percent of the human genome. Locating the noncoding but functional sequences throughout the rest of the genome is the main mission of the ENCODE (**ENC**yclopedia **O**f **D**NA **E**lements) research consortium. NIH also has pressed ahead with the Model ENCODE project (modENCODE) 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.*[63] The strategy is to identify genomic mechanisms in these model organisms, which will elucidate novel research directions for human genomic and other researchers.

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. As NIH continues to fund technological innovation in this area, the costs continue to fall remarkably. 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. The practice of medicine will move beyond a one-size-fits-all approach, and the promise of personalized medicine will be realized.

NHGRI's 1000 Genomes Project aims to discover almost all human genetic variants in order to support studies relating genetic variation to health and disease. The project is sequencing the genomes of 2,661 people from 26 populations around the world and releasing the data publicly. The sequence data will allow the project to identify variants ranging from single DNA base differences among people up to large insertions or deletions in their genomes. Many of these variants contribute to an increased risk for particular diseases or to differences in drug response. Researchers will use these data to map the genes and variants affecting disease and to study the genetics of human populations.

Research in the area of 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 Pharmacogenetics Research Network (PGRN) is to better understand the genetic basis for variable drug responses and identify safe and effective drug therapies designed for individual patients.

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.

[63] Celniker SE, et al. *Nature* 2009:459(7249):927–30. PMID: 19536255.

When the Human Genome Project was completed in 2003, the cost to sequence a human genome was more than $10 million. NHGRI understood that human genome sequencing, far from being over, was just beginning. Conducting the research needed to dissect genomic contributions to disease would require hundreds of thousands to millions of human sequences. Lowering the cost became a high priority, so NHGRI set a goal of reducing the cost of sequencing a human genome to $1,000 in 10 years, with an intermediate goal of $100,000 in 5 years. Since launching the Advanced DNA Sequencing Technology program in 2004, NHGRI has committed more than $150 million to 60 research teams and supported a wide variety of scientific approaches. By 2009, NHGRI-supported research had contributed to achieving the five-year goal. The resulting technologies have revolutionized the study of human genetic variation in studies ranging from the 1000 Genomes Project to The Cancer Genome Atlas. The focus of the sequencing technology program has shifted toward achieving human genome sequencing for $1,000 or less, which will offer the possibility of using genome sequence information in a routine healthcare setting.

Using DNA from tissue samples, genome-wide association studies scan and compare entire genomes of people with and without a particular disease, looking for single-base differences (known as single nucleotide polymorphisms, or SNPs) that might signal the presence of a gene or some other functional sequence implicated in the disease. GWAS are based on the Haplotype Map (HapMap) of the human genome, produced via an NIH-led international research team earlier in the decade that identified more than 3 million relatively common SNPs in human genomes that serve as markers for larger neighborhoods of DNA sequences.[64] GWAS scans point to regions of the genome that are worthy of closer study in seeking the genetic cause of a disease. Over 1,600 of such studies have been conducted since the technique was first developed in 2005, flagging genetic areas that may be linked with at least 80 different diseases and disorders including heart disease, diabetes, obesity, inflammatory bowel diseases, and many types of cancer.[65]

Information emerging from NIDCR investments in GWAS of dental caries complements other clinical research on caries risk factors, allowing genetic factors to be considered, along with behavioral, environmental, and microbial determinants of caries development, when treatment decisions are made. Molecular-based oral health care will transform the most fundamental principle of the dental profession —restoration of form and function—as dentists will use the precision of individual genetic and physiological information as their operational guide. In addition, a recent GWAS of cleft lip and/or cleft palate,[66] the fourth most common birth defect, is providing insight into genetic variants and their interplay with non-genetic factors, which may lead to improved prevention and treatment strategies. NIDCR is also supporting efforts to identify the genetic component of areas critical to diverse patient groups, such as Sjögren's Syndrome and periodontal disease. NIDCR investments are catalyzing tremendous progress in understanding the role of genetic variation in a wide range of conditions such as craniosynostosis (premature closing of joints between bones in the skull) using more targeted genotyping, DNA sequencing, gene expression studies in tissues, and animal models of human

[64] For more information, see http://www.hapmap.org/.
[65] For more information, see http://www.genome.gov/gwastudies/.
[66] Beaty TH, et al., *Nat Genet.* 2010;42(6):525–9. PMID: 20436469.

conditions. These investments are laying the groundwork for translation of compelling clinical leads into improved, individually tailored care.

While the genetic causes of most diseases and disorders are not fully understood, NIH researchers have identified individual genes or regions of DNA associated with numerous diseases and disorders, such as schizophrenia and bipolar disorder; cancers of the skin, lung, brain, pancreas, breast, prostate, and testicle, and acute lymphoblastic leukemia; diabetes; periodontitis in African Americans; asthma; high blood pressure; heart arrhythmias; inflammatory bowel diseases; kidney disease; Alzheimer's disease; and obesity, among many others.

NIH completed full sequencing and analysis of multiple vertebrate and invertebrate animal genomes over the past four years. These include the platypus, domestic cattle, the wasp, other insects, and a large number of disease-causing organisms—such as the malaria-causing parasite *Plasmodium vivax,* the common intestinal parasite *Giardia lamblia*, the Lyme disease-causing tick *Ixodes scapularis*, and two species of the parasitic flatworms that cause schistosomiasis. Also sequenced were thousands of separate strains of the constantly changing human influenza viruses. NIAID now has sequenced the genomes of thousands of infectious microorganisms, including 10,000 influenza viruses.

NIH-funded analysis of genomic data from 121 African populations, 4 African American populations, and 60 non-African populations revealed that all African populations descended from 14 ancestral groups. Most African Americans trace the majority of their ancestry to West Africa, a finding that will improve scientists' ability to identify genetic risk factors in African and African American populations.

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 is 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 NIH Common Fund Epigenomics Program aims to stimulate research to understand the role of epigenetic regulation of gene expression in the origins of health and susceptibility to disease. It is anticipated that this program will transform biomedical research by developing comprehensive reference epigenome maps, identifying novel epigenetic marks, and developing new technologies for

comprehensive epigenomic analyses. In addition, new lines of research are aimed at understanding how environmental exposures may work through epigenetic mechanisms to affect susceptibility and development of disease. Ongoing epigenomic projects include studies on cognitive decline, atherosclerosis, and effects of bisphenol A exposure.[67]

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 beneficial—species that actually perform necessary cellular functions (such as the digestion of certain nutrients in the intestines). Through the NIH Common Fund, the Human Microbiome Project 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. For example, microbial communities may contribute to such diseases and conditions as obesity, diabetes, cancer, and autoimmune diseases. Sequencing technology has, as with human genomics, speeded the study of the microbiome considerably. NHGRI and other NIH ICs are using sequencing technology, among other methods, to study bacterial species in and on the human body. However, other high throughput technologies offer the potential to enrich our understanding of the contribution of the microbiome. The Common Fund is supporting studies to explore the utility of these approaches.

Dovetailing with this effort, NIDCR-supported researchers and others recently identified the more than 600 distinct microbial species that are residents of the human mouth. NIDCR-supported researchers have gathered this information in the Human Oral Microbiome Database (HOMD), the first example of a curated human body site-specific microbiome resource which is freely available to the public. Advances in studying oral microbial communities have the potential for rapid impact on research for new, more personally targeted, clinical treatment. For example, researchers have identified a microbe called *Scardovia wiggsiae* that appears to be linked with severe forms of early childhood caries.

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. 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

[67] For more information, see http://nihroadmap.nih.gov/epigenomics/fundedresearch.asp.

with disease progression, researchers can then use hypothesis-driven basic research experiments to further understand how particular proteins and molecules function in the pathways.

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 Structural Biology Roadmap is a strategic effort to create a "picture" gallery of the molecular shapes of proteins in the body. 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.

Glycomics

NIH is also mapping out additional molecular compounds associated with cellular function. In one field, NIH is seeking 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, 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.

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.

To support initiatives in this area, NIH has established National Centers for Systems Biology. At 10 interdisciplinary centers, NIH-funded 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. The Program in Systems Immunology and Infectious Disease Modeling, a component of NIH's intramural research program, seeks to apply a

systems biology approach to characterize a complex biological system: the human immune system. In this effort, researchers are seeking to develop models that enhance our understanding of the molecular basis for an immune response to infection or vaccination. The NIH Integrative Cancer Biology Program (ICBP) 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 the 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, at the molecular level, how these agents impart immune system dysfunction could offer potential therapeutic targets for treating these disorders.

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.[68] Health-injuring behaviors such as smoking, drinking, and drug abuse, as well as inactivity and poor diet are known to contribute to many common diseases and adverse health conditions. Unfortunately, there are few tried and true approaches to motivate people to adopt and maintain healthy behaviors over time.

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.

[68] Schroeder SA. *N Engl J Med*. 2007;357(12): 1221–8. PMID: 17881753.

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, and developmental) that shape health decision-making and the conditions under which knowledge leads to action vs. 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 NIH Common Fund launched the Science of Behavior Change program to improve our understanding of human behavior change across a broad range of health-related behaviors. The program now supports research that integrates basic and translational science and cuts across disciplines of cognitive and affective neuroscience, neuroeconomics, behavioral genetics, and behavioral economics. The program aims to establish the groundwork for a unified science of behavior change that capitalizes on both the emerging basic science and the progress already made in the design of behavioral interventions in specific disease areas.

Also launched in FY 2010, the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) is a trans-NIH initiative supported and managed by 24 ICs and four program coordination Offices within the OD. Its mission is to pursue opportunities for strengthening basic behavioral and social science research at the NIH while innovating beyond existing investments. In FY 2010, OppNet funded short-term, mentored career development awards in the basic behavioral and social sciences for mid-career and senior investigators, and competitive revisions in basic behavioral and social sciences research, HIV/AIDS-related research and Small Business Innovation Research and Small Business Transfer Technology Research Grants. In FY 2011 OppNet funded new awards to support basic research on the following topics: self-regulation; the effects of the social environment on health; sleep and the social environment; psychosocial stress; and basic mechanisms influencing behavioral maintenance. In addition, the initiative supported short- term, interdisciplinary research education programs for new investigators, scientific meetings to foster the development of interdisciplinary research teams, additional competitive revisions, and short term, mentored career development awards. By fostering basic research on behavioral and social processes, OppNet supports the NIH mission 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 the burdens of illness and disability.[69]

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

[69] Additional information about OppNet can be found at http://oppnet.nih.gov/index.

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 interrelationships among the many determinants of health—biological, behavioral, and social—to provide a way to address complex problems within the framework of the "big picture." Systems science involves developing computational models to examine the dynamic interrelationships of variables at multiple levels of analysis (e.g., from cells to society) simultaneously (often through causal feedback processes), while also studying 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 seven multi-institutional research and informatics groups 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 policymakers, 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.

Research Resources, Infrastructure, and Technology Development

In building the foundation for its broad portfolio of basic research programs, NIH also makes significant investments in the development of research resources, infrastructure, and state-of-the-art technologies that facilitate the next discoveries in biomedical and behavioral research. In line with its interest 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, which stores, maintains, and distributes selected lines of genetically engineered mice; the National Stem Cell Bank, which makes human embryonic stem cell lines readily available; and the Beta Cell Biology Consortium, which generates animal models and antibodies that are available to the scientific community for research on type 1 and type 2 diabetes. eyeGENE®, a nationwide partnership of 250 Registered Clinical Organizations, has created a national, open-access DNA repository of genetic samples from highly characterized individuals and families. Serving both research and clinical needs, the Network has broadened accessibility of diagnostic genetic testing through a central and secure process, testing 70 genes in over 30 inherited eye diseases from 3,500 patient samples since its establishment in 2006.

In addition to animal models and research reagents, NIH also supports the distribution of massive amounts of genome sequence, transcriptional profiling, and cellular structure function data for use and analysis by the research community at large. NIH continues to serve as a leading global resource for building, curating, and providing sophisticated access to molecular biology and genomic information. In addition to databases, NIH also provides resources for retrieving, visualizing, and analyzing molecular biology and genome sequence data online.

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-one-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, today 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 dizzying speed. Finally, partnership efforts are significantly changing the research landscape, in part by spearheading the implementation of scientific projects that no one party would be able to perform independently.

NIH is uniquely 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.

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 (e.g., pharmaceutical companies, nonprofit organizations). Specifically, NIH supports translational studies unlikely to garner substantial investment by other sources because of insufficient financial incentives—for example, 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 which 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 and play important roles in the diagnosis of disease, the identification of patient populations that could benefit from particular therapies, and the monitoring of treatment effectiveness.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an example of an innovative public-private partnership to develop uniform standards for acquiring longitudinal, multisite biomarker data, including magnetic resonance imaging (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 2010, ADNI entered its second major five-year phase (ADNI 2) focusing on participants who exhibit the very beginning stages of memory loss. One important aspect of the study is the data will be posted to a publicly accessible database and available to qualified researchers worldwide. This initiative will speed the pace of discovery by providing a centralized resource allowing investigators to access, study, and share their own high-quality data relevant to AD.

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 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 for determining more precise strategies to treat those with cancer. Within its Center for Cancer Genomics, the Cancer Genome Atlas 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. This knowledge will ultimately lay the foundation for improving cancer prevention, early detection and treatment. It has recently cataloged the genetic alterations in two important cancers for which early diagnostic methods, broadly applicable prevention strategies, and effective therapies are not yet available: the uniformly lethal brain cancer glioblastoma multiforme and serous ovarian carcinoma.

NHLBI has funded several genome consortia with strong translational components. Research focuses include the identification of genetic variants that may explain why some people with asthma do not benefit from inhaled corticosteroids, gene and chromosomal variations that affect pulmonary fibrosis risk and cystic fibrosis severity, improving outcome prediction for myelodysplastic syndromes, identification of genetic factors that influence blood pressure, and development of 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 towards 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) 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* (iPOP) 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 Clinical Center, the trial, dubbed "ClinSeq" (*Clin*ical *Seq*uencing), has enrolled 900 patients to date with a spectrum of coronary artery calcification, from normal to diseased, and will sequence 200–400 areas of their DNA that contain genes suspected of involvement in heart disease. 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 ages 25–40 are 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.[70] Those who are offered the testing use an interactive, Internet-based program designed by NHGRI researchers that helps participants ask questions about the genetic testing, get information, and decide whether to receive the testing. Meanwhile, Multiplex Initiative researchers monitor the participants' decision process every step of the way. Those who decide to submit blood samples for the tests will be followed for some time in order to see whether they change their behavior (e.g., by adopting a healthier lifestyle or diet) in response to their test results.[71] Researchers involved with this study have found that individuals who discuss their genetic information with their doctors may be among the most motivated to take steps toward more healthy choices.

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. As the baby boomer generation continues to celebrate milestone birthdays, improving the health of older Americans is more important than ever. The goal of

[70] For more information, see http://www.multiplex.nih.gov/.
[71] For more information, see http://www.genome.gov/pfv.cfm?pageID=25521052 and http://genome.gov/pvf.cfm?pageID=25521955.

the centers is to improve the health, quality of life, and productivity of middle-aged and older people. The centers work to facilitate translation of basic behavioral and social science to practical outcomes by developing new technologies and by stimulating new use-inspired research (that is, research focused on meeting a societal need, usually for a device to improve quality of life for certain populations). Roybal investigators have made several key discoveries. For example, researchers have developed tools and technologies for identifying older adults at risk for automobile crash involvement, and are working with industry partners to develop and disseminate products based on these tools. Additionally, researchers have developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Several centers will 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 financial well-being while reducing costs, and foster translation of approaches from behavioral economics to the improvement of health care delivery for older adults.[72]

Clinical and Translational Science Awards

The Clinical and Translational Science Awards (CTSA) program supports collaborative teams of investigators representing diverse specialties to tackle complex health and research challenges and accelerate translation of discoveries into treatments for patients. The consortium of 60 medical research institutions across the nation enables innovative research teams to speed discovery and advance science aimed at improving our nation's health. The program encourages CTSA-initiated changes in research infrastructure, including coordinated programs to train and educate early-stage clinical and translational scientists, and development of bioinformatics programs to manage medical record data and transform institutional research activities and resources into searchable databases. The teams are making progress across a broad range of diseases and conditions, such as cancer, diabetes, neurological disorders, and heart disease. CTSA resources to foster translational research include *i2iConnect,* a database of industry contacts looking for new ideas and products that researchers and other innovators can search quickly by specialty and disease area to find potential industry partners interested in their work; *CTSA-IP*, an online intellectual property search engine that aggregates and promotes technologies from CTSA institutions and NIH to enhance research activity and encourage private partnerships; and the *CTSA Pharmaceutical Assets Portal*, which enables scientists to learn more about compounds evaluated for specific diseases that might be used to treat other conditions.

Examples of CTSA-enabled Translational Research Advances

Researchers at the Scripps Translational Science Institute and the University of California, San Diego, Clinical and Translational Research Institute invented a new technique to investigate and help identify risk for coronary artery disease (CAD). They discovered variations in the DNA in one area of the genome that changed the way a gene in a totally different area functioned, thus increasing CAD risk. This discovery opens the door to new interventions that could one day predict heart attacks before they happen and may lead to insights into other conditions linked to poorly understood genetic risk factors.

[72] http://www.nia.nih.gov/newsroom/2010/02/nia-funds-roybal-centers-translational-research-aging

Pilot research by a team at The Ohio State University Center for Clinical and Translational Science indicates that oxygen therapy can protect rodent brain cells during stroke, when a blood clot blocks the flow of oxygen-rich blood to the brain. In the study, the team found that oxygen therapy could reduce brain damage when given during a stroke but was less effective after surgeons removed the blockage, pointing to the need to begin the therapy soon after stroke onset to achieve the best results.[73] These findings easily could lead to a new therapy, because providing oxygen to stroke patients would be simple and fast.

[73] Rink C, et al., *J Cereb Blood Flow Metab.* 2010;30(7):1275–87. PMID: 20145654.

Clinical Research

NIH places a high priority on clinical research as it is the primary source of insights about new means for reducing the burden of illness and improving public health. Clinical research is patient-oriented research that is conducted with human subjects (i.e., research that 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 keep 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* to help people learn more about clinical trials, why they matter, and how to participate (*see Information at the Service of Health on page 76*).

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's ICs oversee a broad portfolio of clinical research that encompasses intramural and extramural programs.

Clinical Resources and Programs

As described in the previous section, the CTSA program supports a national consortium of medical research institutions that are transforming the way biomedical research is conducted. Its goals are to accelerate the translation of laboratory discoveries into treatments for patients, to engage communities in clinical research efforts, and to train a new generation of clinical and translational researchers. Launched in 2006 by NIH, the CTSA program has enabled innovative research teams to speed discovery and advance science aimed at improving our nation's health. The CTSA program encourages collaborative teams of investigators to tackle complex health and research challenges and then find ways to turn discoveries into practical solutions for patients. These teams are already making progress across a broad range of diseases and conditions, such as cancer, diabetes, neurological disorders, and heart disease. They also work with industry, manufacturers, patient groups, and nonprofit organizations to ensure that potentially life-saving new drugs and devices reach the public faster.

CTSAs provide a foundation for clinical and translational research by providing specialized infrastructure support to NIH-funded scientists, engaging community partners to connect scientists with those who both are underrepresented and could benefit from research, and helping to train the next generation of clinical and translational scientists. In addition, they provide tools and resources such as ResearchMatch, a secure electronic volunteer recruitment registry to provide individuals nationwide with opportunities to be considered for participation in research studies and clinical trials.[74]

Examples of CTSA-enabled Clinical Research Advances

Stanford University's Biodesign program trains interdisciplinary groups of graduate students in medicine, engineering, and business in the skill of medical "inventorship" and provides small proof-of-concept grants for projects with high potential to improve patients' lives. Several new devices the students have created through this program, partially supported by the Stanford Center for Clinical and Translational Education and Research, are now being brought to market. These include a ventilator prototype designed for use during natural disasters, and the first inexpensive, natural-motion prosthetic knee for leg amputees in resource-poor countries.

With funding through the Translational Tool Pilot Program and Clinical Research Scholars Program at the University of Pittsburgh Clinical and Translational Science Institute, investigators have developed a device to translate brain commands into actions for assisted devices, potentially improving quality of life for patients disabled by spinal cord injury, stroke, or neurodegenerative disease. The device recently received FDA and institutional review board (IRB) approval to study brain control in individuals with paralysis. The ultimate aim is to close the gap for paralyzed patients between what they wish they could do and what they can do.

[74] For more information, please see: www.researchmatch.org.

A powerful research collaboration with the Scripps Translational Science Institute, the West Wireless Health Institute, wireless device manufacturers, and the CTSA consortium is enabling researchers to conduct large-scale studies to discover how wireless devices, many the size of a small adhesive bandage, can be used to improve patient health and reduce health care costs.

NIH Clinical Center

The majority of NIH clinical research takes place at teaching hospitals around the country and overseas. Approximately 1,500 studies, however, take place at the NIH Clinical Center in Bethesda, Maryland at any given time. The NIH Clinical Center 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 Clinical Center is now one of the largest federal buildings in the Washington, D.C. metropolitan area.

The NIH Clinical Center is the nation's largest hospital devoted entirely to clinical research. Each year, the Clinical Center serves more than 10,000 new patients and 6,000 inpatients and supports over 95,000 outpatient visits. In addition to the approximately 1,200 credentialed physicians, dentists, and post-doctoral researchers, it houses over 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 more than 400,000 clinical research participants. Because the Clinical Center is a research facility, only patients with the precise kinds or stages of illness under investigation are admitted for treatment. There are no labor and delivery services and no other services common to community hospitals. All patients must be referred by their physicians.

The Clinical Center, 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 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 ORDR, the Clinical Center hosts the Undiagnosed Diseases Program (UDP), through which individuals with longstanding medical conditions that elude diagnosis by physicians elsewhere can come for consultation. This trans-NIH program has two main goals, which are to provide answers to patients with mysterious conditions that have long eluded diagnosis and to advance medical knowledge about rare and common diseases.

Over 326 cases have been accepted into the program. After its first two years of work, the UDP is citing successes in patients whose cases have stumped specialists at leading medical institutions around the country.[75] Furthermore, the UDP announced the program's first discovery of a new disease, called ACDC, or arterial calcification due to deficiency of the protein CD73, in the *New England Journal of Medicine*. CD73 produces a small molecule, adenosine, that protects arteries from calcifying. A report on an

[75] For more information, please see: http://www.nih.gov/news/health/oct2011/nhgri-06.htm.

additional new disorder is pending publication. Such discoveries could have implications for people with more common diseases and disorders.

In recognition of some of its achievements, the Clinical Center received the 2011 Lasker Public Service Award for creating a research hospital where doctors develop innovative therapies and explore new ways to diagnose, treat, and prevent a wide variety of diseases.

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 the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), a new neurology clinical trials network that will offer shared infrastructure and expertise across neurology diseases. These centralized resources will include support for patient recruitment into trials, protocol-development assistance, and a central IRB, which are expected to expedite trial start-up time. The network will reduce delays in building infrastructure for each new trial, improve the speed of enrollment of trial participants, and enable better choices of therapies for Phase III trials.

NIH and NCI are 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 Cooperative Group clinical trials by enabling 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.

NHLBI launched a major clinical trial to test a gene-based method of prescribing warfarin, a blood thinner that is widely used to prevent life-threatening blood clots. About 2 million Americans start taking warfarin each year, but the drug's effect can vary significantly from one patient to another. Regular blood tests are needed to both establish an initial dose level and maintain the proper level as time goes on—for months and often for years. In early 2009, an international research consortium combined patients' genetic and clinical data to produce a computer algorithm for initial dosing that appeared to be more accurate than dosing based on a patient's clinical condition alone, and then increased or decreased the dose to achieve the optimal blood level. NHLBI launched the multicenter Clarification of Optimal Anticoagulation through Genetics (COAG) clinical trial[76] to compare the gene-

[76] For more information, see http://coagstudy.org/.

based method with the current trial-and-error approach in a much wider pool of patients. COAG will enroll 1,200 patients of varying backgrounds at 12 sites and follow them for four years. Its outcome could improve protection against heart attacks and strokes for millions of Americans.

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 is also 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 its 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 33,000.

Maximizing human subject protection, while facilitating translational and applied clinical research, has become a critical challenge in the 21st century. To increase the efficiency and effectiveness of the clinical research enterprise, NIH is examining barriers to clinical research and striving to harmonize regulations and policies that pertain to its conduct and oversight. As the lead federal agency supporting clinical research, NIH has an obligation to promote the efficiency and effectiveness of the clinical research enterprise by facilitating compliance and oversight.

NCI is implementing changes to its Cooperative Groups Clinical Trials Program that will improve efficiency, oversight, and collaboration of trials, as recommended in an April 2010 Institute of Medicine report. These changes include consolidation of the adult clinical trials groups; standardization of clinical trials data management software for NCI-sponsored multi-site trials; acceleration of clinical trial activation through the implementation of a real-time, internet-based dashboard containing clinical trial information for all parties involved in the process; collaboration with FDA scientists in NCI's disease-specific scientific steering committees; standardization of language for clinical trial and intellectual property agreements; improving funding of studies and increasing incentives for patient and physician participation by increasing per case reimbursement rates; and developing a credentials registry for investigators and clinical trial sites.

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/biotechnology companies and academic medical centers. In addition, NCI’s Clinical Trials Reporting Program is establishing a comprehensive database containing regularly updated information on all NCI-funded interventional clinical trials. Grantees are requested to enter specific information about each clinical trial into the database. This information will be used to coordinate research efforts to optimize the nation’s investment in cancer research.

Collecting and sharing clinical research data requires large investments in time and resources, yet currently there is no uniform way to help investigators implement NIH data-sharing policies for research on neurological disorders. In 2006, NINDS initiated an effort called Common Data Elements (CDEs)[77] to address this issue for many different disease areas. NINDS has worked with disease-specific experts and other stakeholders as part of this effort 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 data elements, and disease-specific elements for headache, spinal cord injury, stroke, epilepsy, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, Friedrich's ataxia, and multiple sclerosis, all of which are available on the website for use by investigators. A working group is currently developing data elements for several neuromuscular diseases, such as spinal muscle atrophy, Duchenne muscular dystrophy, traumatic brain injury, and myasthenia gravis.

Sometimes it is not clear which treatment or intervention is best for a patient in a given circumstance. NIH plays a critical and unique role for patients by sponsoring and funding research that compares different interventions or strategies to prevent, diagnose, treat, and monitor health conditions in real-world settings. 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 recently published CER trial compared Lucentis, a drug developed by Genentech to treat wet age-related macular degeneration (AMD), and Avastin, a structurally related yet significantly less costly drug, also from Genentech, approved by the FDA for some cancers but commonly used 'off-label' for AMD. The two-year NEI-funded study found the drugs were equally effective for improving visual acuity, providing doctors and patients more options for treating AMD. Given that most AMD patients are over 65, CATT findings have important implications for Medicare spending; the US Office of the Inspector General (OIG) issued a report in September 2011 stating that Medicare would have saved $1.4 billion in 2010 if all AMD patients had received Avastin.

One of the most visible means by which NIH reaches, engages, and informs the patient and medical health professional communities is through the congressionally mandated ClinicalTrials.gov Web site. To enhance enrollment and provide a mechanism for tracking the progress of clinical trials, the FDA Amendments Act of 2007 [FDAAA, P.L. 110-85] requires "responsible parties" (sponsors or designated principal investigators) to register certain "applicable clinical trials" of FDA-regulated drugs, biological products, and devices with ClinicalTrials.gov no later than 21 days after enrolling the first subject and to submit summary results information, including adverse-event information, no later than 12 months after the completion date of the trial if the drug, biological product, or device under study is approved, licensed, or cleared by FDA.

ClinicalTrials.gov provides patients, family members, health care professionals, and other members of the public easy access to information on clinical studies on a wide range of diseases and conditions. The information is provided and updated by the sponsor or principal investigator of the clinical study and the Web site is maintained by the NLM at NIH. It has been integral to the implementation of policies and

[77] For more information, see http://www.commondataelements.ninds.nih.gov/#page=Default.

other efforts to increase the transparency of clinical research. It serves as a unique, publicly accessible resource that enables users to: 1) search for clinical trials of drugs, biologics, devices and other interventions (e.g., by condition, intervention, or sponsor) and obtain summary 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 have been 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, MEDLINE citations, congressional documents, and press releases.

The existing ClinicalTrials.gov system was expanded by NIH to accept the registration and results information required to be submitted under FDAAA, making it the largest, most heavily used public research registry and results database in the world.

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 don't 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 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. 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.[78] In accordance with the inclusion policy, investigators are required to describe what populations will be included in the proposed study, justify the exclusion of specific groups, and provide planned enrollment data. Scientific Review Groups assess proposed clinical research studies, consider whether sufficient information is provided about planned enrollment, and determine whether the recruitment and retention strategy is realistic. Investigators are also required to report annually their cumulative enrollment data indicating the sex/gender, race and ethnicity of participants in each funded clinical research study. Inclusion enrollment data collected by each IC are compiled into the annual aggregate comprehensive report titled *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research.*[79] The 2011 report indicates that in FY 2010, women constituted 56.1 percent of the 23.3 million participants in clinical studies, and 32.1 percent of participants identified themselves as members of an underrepresented race and/or ethnicity.

Over the past two years, NIH has focused on analyzing and streamlining the data reporting process, reemphasizing the vital role of NIH staff in monitoring adherence to the NIH inclusion policy and management of grants, contracts, cooperative agreements, and intramural research projects involving human subjects. The role of peer reviewers and investigators in meeting policy requirements continues to be emphasized.

[78] For the full report, see http://grants.nih.gov/grants/funding/women_min/women_min.htm.
[79] For the full report, see http://orwh.od.nih.gov/research/inclusion/reports.asp.

Postclinical Translational Research

Postclinical translational research ensures that evidence-based interventions are broadly applied and accessible to those who need them most. NIH 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, financing systems, organizational structures and processes, health technologies, and personal beliefs and behaviors affect access to and utilization of healthcare, the quality and cost of healthcare, and ultimately our health and well-being. The goals of health services research are to identify the most effective ways to organize, manage, finance, and deliver high-quality care.[80]

NIH undertakes a number of activities to ensure that the rich evidence base created through basic and clinical research is translated and utilized to enhance health and reduce the burdens of illness and disability. The focus of health services research supported by NIH 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.

Health services research at NIH addresses topics such as institutional and organizational influences on health, including studies of the organization of and access to health care; its effectiveness in real world settings; its cost efficiency; and its social and cultural acceptability. It may also involve research related to macroeconomic phenomena (e.g., business cycles), community and neighborhood organization, and the structure and functioning of families, as well as how these variables influence the consumption and choice of health care and decision-making concerning health procedures. Finally, this category includes research on how successful approaches to the organization and delivery of health services can be translated into public policy.

Partnering with Health Care Delivery Organizations

Healthcare 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 healthcare 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 healthcare delivery organizations offer, such as electronic medical records for thousands of patients. Already a number of NIH Institutes support collaborative activities between healthcare delivery organizations such as health maintenance organizations (HMOs), and biomedical researchers to implement large studies with real-world benefits.

[80] Report of the Blue Ribbon Task Force on Health Services Research at the National Institute on Drug Abuse, 2004 http://ww2.drugabuse.gov/about/organization/nacda/HSRReport.pdf.

Tackling real-world clinical issues and generating evidence that will be of immediate value to practitioners and patients is the central goal of the NIDCR-supported dental Practice-based Research Networks (PBRNs). Conducting research in dental practices draws on the experience and insight of practicing clinicians to help identify and frame research questions. Because PBRN studies address practice-based problems, their results tend to be more quickly translated into daily clinical care.

Leveraging the infrastructure of established dental practices for conducting PBRN studies also can be a powerful and cost-effective means to conduct clinical research. For example, the past decade brought reports that people who take bisphosphonates, a class of drug prescribed for osteoporosis or to treat the bone-wasting effects of cancer, can develop osteonecrosis (bone death) of the jaw. To address the problem, the three regional PBRNs, taking advantage of their presence in practices spanning multiple states, teamed up to carry out a collaborative study on osteonecrosis of the jaw. The study results, published in 2010, confirmed that bisphosphonate use is a risk factor for osteonecrosis of the jaw, and provided additional important evidence to guide clinicians in their treatment of this challenging condition.

The NCI HMO Cancer Research Network (CRN) consists of the research programs, enrolled populations, and data systems of 14 HMOs nationwide that, collectively, provide care to almost 11 million individuals. Co-funded by the Agency for Healthcare Research and Quality, 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, multi-center, 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 utilizes standardized approaches to data collection, data management, and analysis across health systems. CRN activities have generated more than 140 journal publications in a range of disciplines.

In FY 2010, NIMH launched a major initiative, the Mental Health Research Network (MHRN), which connects nine established public domain research centers based in integrated, not-for-profit health care systems. These systems provide care to a diverse population of 10 million people in 11 states, and they share rich and compatible data resources to support a wide range of effectiveness research. Researchers have begun to use this network to address several important issues, including the development of a geographically and ethnically diverse autism spectrum disorder research registry; a pilot study for a new type of therapy for postpartum depression; and, a longitudinal analysis of how suicide warning labels on antidepressants affect later suicide among youth.

A new initiative of the NIH Common Fund in FY 2010, the Health Care Systems Collaboratory builds on these kinds of investments to create a large infrastructure that leverages the resources of healthcare delivery organizations to implement pragmatic research studies in real world health care delivery settings. This program develops networks of Health Care Delivery Systems to provide a framework of implementation of methods and best practices that will enable the participation of many health care systems in clinical research.

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, NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN) and the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) to enhance the implementation of evidence-based substance abuse and HIV screening and treatment interventions in community treatment programs and the criminal justice system, respectively. 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 stakeholders, which is then integrated to improve drug abuse and addiction treatments, making them more feasible and readily available to those who need them. Similarly, CJ-DATS tests evidence-based approaches and innovative implementation strategies within the criminal justice system as well as upon re-entry into the community.

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To date, nearly 1,000 practitioner-investigators have participated in network projects, and over 30,000 patients from their practices have been enrolled in more than 30 different PBRN studies. These studies include comparisons of the benefits of a variety of dental procedures, dental materials, and diagnostic strategies for patients with diverse clinical conditions. Individual studies have addressed, for example, controlling pain associated with root canal therapy, improving dental restorations, and testing the feasibility of measuring blood glucose levels in dental practice.

In another example, the NIDDK supports translational research efforts to develop affordable, scalable adaptations of the landmark Diabetes Prevention Program (DPP) clinical trial, which found that a lifestyle intervention could prevent or delay type 2 diabetes by 58 percent in people at risk. While the original DPP lifestyle intervention was found to be cost-effective, providing it to a significant fraction of

the 79 million Americans estimated to have pre-diabetes requires still greater efficiency. The positive effects of the DPP continue as new research, building on the study's results, seek the most effective ways to prevent, delay, or even reverse diabetes. Subsequent NIDDK-funded translational research efforts utilized local Ys (formerly YMCAs) for delivering a group-based adaptation of the DPP lifestyle intervention. A pilot study showed that this group-based approach reduces costs to deliver the intervention, while achieving similar levels of weight loss in participants; a larger trial is ongoing. Based on evidence from this clinical and translational research, the CDC, in partnership with the Y and UnitedHealth Group, launched the National Diabetes Prevention Program.[81] Efforts to scale and sustain the National Diabetes Prevention Program continue as a growing number of programs offer the lifestyle change program nationwide. Organizations offering a lifestyle change program consistent with the *Diabetes Prevention Recognition Program Standards and Operating Procedures* can participate in CDC's Diabetes Prevention Recognition Program. Organizations are recognized by CDC for achieving results that are consistent with what research showed to be effective in preventing type 2 diabetes.

In addition, the NIH Office of Medical Applications of Research[82] works closely with ICs to assess, translate, and disseminate the results of biomedical research that can be used in the delivery of health services. OMAR coordinates periodic consensus conferences with the goal of reviewing areas of NIH-supported research where there may be a gap between research accomplishments and clinical care. To date, NIH has conducted more than 120 consensus development conferences and 30 state-of-the-science conferences. Consensus and state-of-the-science statements are disseminated widely after the conference either to modify clinical practice when evidence strongly supports using or not using a particular intervention or to direct future research when important gaps in knowledge have been identified. The consensus statements that result from these conferences are shared widely with healthcare providers, policymakers, patients, and the media.

Health Economics Research

Economic factors are major drivers in healthcare delivery and thus affect the translation of biomedical research findings into health improvements. NIH supports research designed to understand these factors, such as, for example, financing and reimbursement issues related to the adoption and sustainability of newly developed interventions. Under the Common Fund, the Health Economics Program aims to support basic and applied research to understand how innovations in treatments, diagnosis, and preventative strategies can be most effectively implemented in a health care setting, so that past and future investments by NIH may have greater impact.

Results from health services research can inform the entire healthcare sector (clinicians, hospitals, insurers, public health and community centers, and policymakers) about the most efficient and effective means of preventions, screening, and treatment, and opportunities for improvement.

[81] For more information, see http://www.cdc.gov/diabetes/prevention/.
[82] In 2012, the Office of Medical Applications of Research combined resources, staff, and key activities within the Office of Disease Prevention.

Information at the Service of Health

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 the NIH is based on peer-reviewed, cutting-edge science and is designed to meitsc\whiet the needs of the community as well as to be easily accessed and understood. One primary goal of NIH communications efforts is to maintain relevance and credibility with target audiences amid rapidly changing expectations and media formats. Products are also designed to reach audiences who are more affected by a specific risk, disease, or disorder. Through their 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. The ultimate goal is to broaden participation in research and improve health outcomes, especially in medically underserved communities.

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 2011 NHLBI released the Integrated Guidelines for Cardiovascular Health and Risk reduction in Children and Adolescents, which contains evidence-based recommendations on the prevention and management of risk factors for cardiovascular disease, and is directed toward all primary pediatric care providers—pediatricians, family practitioners, nurses and nurse practitioners, physician assistants, and registered dietitians. In another 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 and MedlinePlus en español Web sites, and they are distributed to the public via doctors' offices nationwide.

The Challenge of 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 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.

Trans-NIH Spotlight: Clinical Research Awareness

To address these issues, NIH IC communicators, under the direction of the NIH Office of Communications and Public Liaison (OCPL), are working to raise awareness among the general public and the medical community 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. NIH recently launched the cornerstone of a new crosscutting program, a Web-based educational site called *NIH Clinical Research Trials and You*, developed to help people learn more about clinical trials, why they matter, and how to participate. In launching the Web site (http://clinicalresearch.nih.gov/), NIH Director Francis S. Collins, M.D., Ph.D., said, "The ability to recruit the necessary number of volunteers is vital to carrying out clinical research that leads to health and medical advances. This new, centralized resource will make it much easier for the public and health professionals to learn about clinical trials and how people can participate in them." Most importantly, resources developed from the *NIH Clinical Research Trials and You* 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 researchers. There are also links on the Web site for locating or enrolling in programs. Health care professionals can 1) read about evidence-based strategies for talking with patients about trials, 2) print audience-tested posters to help promote trials in clinics and offices, and 3) find other clinical trial educational materials.

Clearly there is value to federal collaborations and partnerships with communities and stakeholders involved in and/or affected by NIH research. The *NIH Clinical Research Trials and You* site 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.

NIH is working with schools to incorporate discoveries from clinical research into science education programs. NIH also offers story-based features about clinical research to the media. The 2011 launch of *NIH Clinical Research Trials and You* received coverage by media outlets from Connecticut to California. NIH is developing podcasts and other audiovisual resources, making them free and easily reproducible in media outlets. The agency is also taking this resource to the community, by sharing and promoting the Web site and clinical research at events, such as parenting fairs and employee events and in announcements to state public health departments, requesting that state officials share the resources with their own stakeholders. Recently, NIH, through OCPL and the NIH Office of Science Policy, entered into an arrangement with the American Medical Association (AMA) to promote the NIH Clinical Research Trials and You initiative to the organization's 17,000 member physicians.

Highlighted Institute and Center Communication Programs

Millions of Americans search daily online 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 Institutes and Centers continue to build on their proven track record of award-winning public education and awareness campaigns directed at a variety of audiences. Trans-agency efforts originating from NIH campaigns and clearinghouses are also designed to increase visibility of NIH as a leader in the support and conduct of clinical research in an era of personalized medicine.

A listing of featured health awareness, prevention, and treatment campaigns sponsored by the NIH is online at http://www.nih.gov/icd/od/ocpl/resources/campaigns/. 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.

Alcohol and other drugs. NIAAA sponsors a number of efforts designed to address drinking, including an underage-drinking research initiative, an information campaign focused on college drinking, and the Institute's *Rethinking Drinking* initiative, which features evidence-based information about risky drinking patterns in U.S. adults, as well as support for cutting back or quitting. NIAAA also disseminates evidence-based guidelines to health practitioners for screening and intervening with youth and adults. NIDA sponsors several cutting-edge awareness efforts for different audiences, directed at the costly nationwide drug problem. One core audience for several of NIDA's campaigns is teens. For example, NIDA recently launched an interactive Web-based initiative called *PEERx* to educate teens and help them spread the word about the dangers of prescription drug abuse. In 2010, NIDA launched National Drug Facts Week, a health observance week targeting teens with scientific information to shatter common

myths about drugs. In November 2011, about 165 events were held in 47 states, and more than 166,000 teens received NIDA's teen booklet titled "Drugs: Shatter the Myths." NIDA also continues to promote tools and educational resources for healthcare professionals through its NIDAMED initiative, designed to help clinicians identify patients with substance abuse problems, prevent their escalation to addiction, and refer patients to treatment as necessary.

Aging. A national campaign, *Go4Life*, was developed by the NIA to encourage adults age 50 and older to make exercise and physical activity a regular part of their everyday lives. The interactive *Go4Life* Web site features specific exercises, success stories, motivational tips, and nutrition information. Free materials include print publications, an exercise DVD, and online tip sheets.[83] In addition, NIHSeniorHealth.gov Web site was recently redesigned and updated to accommodate older Americans' increased understanding and use of the Internet. Developed by the NIA and the 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.

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. In 2009, NCI expanded its Smokefree campaign to include a dedicated section and companion Facebook page, specifically targeting women. Included in the program are resources and information to help women integrate smoking cessation into daily life and family matters. NCI also contributed Surviving Cancer—a section devoted to providing resources and information to older adult cancer survivors and their families to the NIHSeniorHealth.gov website.

Children's health. NICHD sponsors a number of programmatic efforts to address children's health. For parents, family members, health care workers, and caregivers, the NICHD *Back to Sleep* campaign offers information kits, professional education materials, and other resources aimed at reducing the risk for sudden infant death syndrome. *Milk Matters* is an NICHD public health education campaign designed to promote calcium for healthy bone growth in tweens and teens.

We Can! is a national education program designed to provide parents, caregivers, and youth with reliable, authoritative information designed to help children ages 8–13 maintain a healthy weight. More than 40 national organizations have partnered with *We Can!* to help spread the program's science-based materials and messages through community outreach, a museum exhibit, in-person training programs, information dissemination, and a new interactive curriculum. Three key behavioral goals form the foundation of *We Can!* program messages—improving food choices, increasing physical activity, and reducing screen time. *We Can!* has grown from 14 founding sites to more than 1,600 communities in all 50 states, Puerto Rico, and 13 countries around the world.

[83] For more information, see http://go4life.niapublications.org/.

Chronic obstructive pulmonary disease (COPD). COPD is the third leading cause of death in the U.S. and is estimated to affect 24 million across the nation, with as many as half undiagnosed. To address this serious lung disease, the NIH developed the *COPD Learn More Breathe Better*® campaign. The program is designed to help at-risk men and women over age 45 recognize the signs and symptoms of COPD and motivate them to talk with their health care providers about testing and treatment options. The campaign also gives health care providers information about incidence, early detection, and treatments. Through a network of 74 national and local partners conducting COPD outreach in 47 states, the program sponsors community-level outreach and events, media outreach efforts, social-media strategies, and continuing development of partnerships.

Diabetes. In collaboration with over 200 public and private partners, the NIDDK and CDC co-led National Diabetes Education Program (NDEP)[84] 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. Campaign materials are tailored for minority groups at high risk of developing type 2 diabetes. The NIDDK's National Diabetes Information Clearinghouse also provide key health information for patients, healthcare professionals, and the general public.

Environmental health. The NIEHS-led Partnerships for Environmental Public Health (PEPH)[85] program 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 local, regional, and national levels.

Eye health and vision. The National Eye Health Education Program (NEHEP), a campaign of NEI, is a public and professional education campaign focused on early detection and timely treatment of glaucoma and diabetic eye disease and appropriate treatment for low vision. The NEHEP contains a series of websites that include information on specific diseases and issues with resources available to patients and the public. The Healthy Vision Program provides the public with information about eye health in order to promoted community outreach, and the Healthy Vision Community Awards Program provides seed money to promote these efforts. The Healthy Eyes Toolkit includes resources and materials to promote public education on vision and eye health and includes fact sheets, e-cards stickers, and web links to promote regular eye exams.

Hearing. In October 2008, NIDCD launched *It's a Noisy Planet. Protect Their Hearing***.** The Noisy Planet campaign is designed to increase awareness among parents of children aged 8 to 12 ("tweens") about the causes and prevention of noise-induced hearing loss, or NIHL. With this information, parents and other caring adults can encourage children to adopt healthy habits that will help them protect their hearing for life.

[84] For more information, see http://ndep.nih.gov/.
[85] For more information, see http://www.niehs.nih.gov/research/supported/programs/peph/index.cfm.

Health disparities. NIH has many outreach activities to address health disparities. For example, the NIAMS Health Partnership Program is a community-based, collaborative research program between NIAMS and Washington, D.C. area community organizations. Through research with underrepresented patients affected by arthritis and other rheumatic diseases, the program studies health disparities and their causes, and provides direction for improving the health status and outcomes of affected minority communities. Its Community Health Center, located in Silver Spring, Maryland, gives the community access to specialized care and health information, and provides NIH researchers with access to patients most affected by rheumatic diseases.

The NIAMS National Multicultural Outreach Initiative, an outgrowth of the NIAMS local Health Partnership Program, aims to help address disparities in the availability and access to research-based and culturally relevant health information among various multicultural groups. Through culturally targeted health planners, 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.

Heart health. In 2011, NHLBI released the Integrated Guidelines for Cardiovascular Health and Risk reduction in Children and Adolescents, which contains evidence-based recommendations on the prevention and management of risk factors for cardiovascular disease, and is directed towards all primary pediatric care providers–pediatricians, family practitioners, nurses and nurse practitioners, physician assistants, and registered dietitians.

Kidney disease. The NIDDK's National Kidney Disease Education Program (NKDEP[86]) is designed to raise awareness about the problem of kidney disease and steps 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. In October 2010, NKDEP hosted a meeting titled "Translating Chronic Kidney Disease Research into Improved Clinical Outcomes." Several planning grants were funded as a result of this meeting.

Oral health and oral cancer. African American men are one of the groups at highest risk for oral cancer, but many don't know it. *Are You at Risk for Oral Cancer? What African American Men Need to Know*, a campaign from NIDCR and NCI, is designed to promote early detection of oral cancer among African American men. Campaign materials include a video, radio PSAs, a brochure, a card describing the oral cancer exam, posters, and a fact sheet. Promotion has involved, for example, distributing campaign kits to African American community cancer programs, sending the PSAs to African American radio stations around the country, and outreach to the press.

Stroke. NINDS continues to develop and manage the Institute's groundbreaking public education campaign: *Know Stroke: Know the Signs. Act in Time*. The campaign was designed to help increase knowledge and 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

[86] For more information, see http://nkdep.nih.gov/.

professionals using mass media, social media, grassroots partnerships and community education. Since 2004, the *Know Stroke* campaign has focused on the grassroots Know Stroke in the Community initiative. The foundation for this initiative is community engagement in "train the trainer" programs in major urban areas across the U.S. using NINDS materials to educate local high risk audiences including African Americans, Hispanics, and people over the age of 50 and their family members, caregivers and health care providers. NINDS has also partnered with the General Federation of Women's Clubs creating a nationwide network of volunteers; and with the National Council of La Raza in the development and promotion of culturally appropriate materials for Spanish audiences including a video, flipchart and toolkit. Going forward, NINDS has initiated a partnership with the AHA to coordinate a national distribution of the NINDS-developed Hispanic education toolkits through health educators and community outreach workers in local communities across the country.

NIH communication strategies and efforts translate scientific findings to be easily accessed and understood for broad audiences. NIH also maintains relevance and credibility with the public by using multiple media formats and design information to reach audiences who are more affected by a specific disease or risk. Throughout changes in health and science communications, NIH communication offices utilize campaigns and clearinghouses to continue to broaden participation in research and improve health outcomes, especially in medically underserved communities.

Harnessing Technology

In today's world, technological advances move at an unprecedented pace. NIH is tapping into 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, and to ensuring that research results—from scientific publications to patient and consumer health information—are readily available to all.

NIH support of technology development continues to trigger revolutions in the 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 today's research 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 utilization of biomedical information systems (i.e., disease registries and other databases) are essential to managing large amounts of data for research, clinical care, and public health. 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 explore 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 make use of similar software applications. NIH is also keenly attuned to the importance and challenges associated with preserving, protecting, and ensuring the validity and security of information stored in biomedical databases.

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 neurology 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 intramural program.

- High-risk, innovative projects with little preliminary indication of the likelihood of success, although they may have a potentially significant impact if successful. These proof-of-principle projects usually have small budgets and short timeframes.

The research pipeline is replete with examples of NIH's commitment to technology development, its foresight in identifying emerging needs and promising areas of investigation, and its ability to foster the development of technology that links basic research with clinical applications.

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, records management, and other related fields.

NIH-supported efforts are affecting how healthcare 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 healthcare decision-making by asking more informed questions about their care. Patients will be able to provide this information to any healthcare provider regardless of where they are located. 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 healthcare 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), may improve how patients provide information on their conditions and how doctors use that information in treatment decisions. An online computer-adaptive testing system, PROMIS records patient reports of symptoms such as pain, fatigue, and emotional distress related to a wide variety of chronic diseases and conditions.

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 have become indispensable national and international resources for biomedical research and public health. Several trans-NIH activities 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 healthcare 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.* Major systems include GenBank for genomic sequence data and dbGaP (database of Genotype and Phenotype) for GWAS data.

- *Disease registries and surveillance systems.* NIH works with other federal and private entities to integrate disease registries for national and local use. For example, the Surveillance, Epidemiology, and End Results (SEER) program in the NCI has been the foundation for innumerable studies, including recent research into links between hormone therapy and breast cancer.

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

- *Standardized vocabularies and data protocols.* NIH leads the government's efforts to develop standardized vocabularies and terminology to support interoperability among biomedical information systems in research and clinical settings.

- *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.

Catalog of Disease Registry, Database, and Biomedical Information System Activities

In response to the mandate under SEC. 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 FYs 2010 and 2011 to develop or maintain databases, disease registries, and other information resources for the benefit of the larger research community.

NIH Scientific Databases: Enhancing Access to Research Information

Keeping pace with the expanding volume of biomedical knowledge is a continuing challenge for scientists, clinicians, policymakers, 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, from the results of scientific or clinical research studies, to genomic information, to standard reference materials (such as genome sequences or anatomical images), and to published journal articles and citations to the medical literature. They are widely used by biomedical researchers, as well as by a growing number of clinicians, public health officials, and consumers. 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 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 database comprises more than 21 million citations for biomedical literature from MEDLINE, life science journals, and online books.

In addition, NIH continues to expand PubMed Central (PMC), 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 now provides public access to more than 2.5 million research articles. Some of this increase is attributable to an expanding scope of user (not just biomedical researchers, but also clinicians, other practitioners, and consumers) that highlights the importance of this type of resource.

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. NIH's PubChem database, for example, houses the voluminous data on molecular structures and functions that is produced through NIH funding under the Molecular Libraries Initiative of the NIH Common Fund. It provides information about the biological activity of small molecules, organized as

three linked databases along with a chemical structure similarity search tool. PubChem now contains more than 35 million unique chemical structures and more than 600,000 bioassays. PubChem is integrated with NIH's Entrez suite of biomedical information resources, an integrated collection of some 40 databases and more than 570 million records of molecular and genomic data. This integration enables users to retrieve related data from multiple databases and navigate among them with relative ease.

Individual Institutes 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 FaceBase Consortium, creating a freely available database compiling the biological and genetic instructions to construct the middle region of the human face. FaceBase will facilitate data production and integration, as well as accelerate translational and clinical application of this knowledge for the prevention, treatment, and management of craniofacial birth defects. FaceBase's individual scientific projects continue to provide data to the FaceBase data integration and management hub; the hub's informatics development team is creating new interfaces for displaying and searching those data on the consortium's Web site, www.facebase.org.

Genomic Information Systems: Understanding the Genetic Basis of Disease

NIH has made great strides in developing information resources to support genetics research. Considerable effort has been aimed at supporting the analysis of data from GWAS, which explore the connection between specific genes (genotype information) and observable diseases or conditions (phenotype information, such as diabetes, high blood pressure, or obesity). NIH's dbGaP (database of Genotype and Phenotype) houses data from a number of GWAS, including those funded by NIH. NIH's GWAS policy 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, NIMH Center for Collaborative Genetic Studies on Mental Disorders, the NIDA Center for Genetic Studies, the NINDS Human Genetics Repository, the NIEHS Chemical Effects in Biological Systems (CEBS) Knowledge Base, and the NIA Genetics of Alzheimer's Disease Data Storage Site 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 collect information about the occurrence of specific diseases, such as cancer and Parkinson's disease, the kinds of treatment that patients receive, 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 policymakers.

Disease registries have been employed for research on autoimmune disorders, including Sjögren's Syndrome, one of the most prevalent. A significant roadblock for moving discoveries ahead in the field of Sjögren's Syndrome is a lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish patient registries at two extramural institutions, as well as through its own intramural program. These groups work together to generate and share genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts with the general research community.

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 (INTERMACS), for example, is a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. The registry is supported jointly by NIH, FDA, and CMS. 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. 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.

NIH continues to update the Unified Medical Language System (UMLS), which is used heavily in advanced biomedical research and data mining worldwide. The UMLS Metathesaurus, with more than 8.6 million concept names from 161 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.

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 easy for investigators to expand a study design beyond the primary research focus.

NIH also supports the Neuroimaging Informatics Tools and Resources Clearinghouse,[87] which finds and compares tools and resources used for analyzing neuroimages such as MRI scans. Tools include software, hardware, and algorithms among others. This resource helps researchers compare and find tools best suited to their research projects. Developers can gain valuable help from the research community to make their tools more usable and accessible.

Large-Scale Informatics Infrastructure

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, for example, which allows for standardized data reporting and sharing of information across clinical studies.

In the area of cancer research, NIH has established the Cancer Biomedical Informatics Grid® (caBIG®), a collaborative information network for all of NCI's advanced technology and program initiatives that aims to enable collaborative research and personalized, evidence-based care. The network connects scientists, practitioners, and patients, enabling the collection, analysis, and sharing of data and knowledge along the entire research pathway from bench to bedside. Specific biomedical research tools under development by caBIG® include clinical trial management systems, tissue repositories and pathology tools, imaging tools, and a rich collection of integrative cancer research applications.

In an effort to support and accelerate research in the prevention, cause, diagnosis, and treatment of research on Autism Spectrum Disorders, NIH created the National Database for Autism Research. This database collects a wide range of data types, including phenotypic, clinical, and genomic, as well as de-identified medical images, derived from individuals who participate in Autism Spectrum Disorders research, regardless of the source of funding. The National Database for Autism Research provides the infrastructure to store, search across, retrieve, and analyze these varied types of data. It also coordinates data access with many other federal databases, such as the NIMH Center for Collaborative Genetic Studies. The center is a national resource for researchers who study the genetics of complex mental and developmental disorders, such as Autism Spectrum Disorders, and stores human DNA, cell cultures, and clinical data. In 2011, the National Database for Autism Research received an HHS*innovates* award, recognizing its outstanding innovation efforts within HHS.

Other efforts aim to provide the informatics infrastructure to advance basic research and clinical studies across the spectrum of biomedical sciences. The CardioVascular Research Grid provides infrastructure for sharing cardiovascular data and data analysis tools. The CardioVascular Research Grid builds on and

[87] For more information, see http://www.nibib.nih.gov/About/Overview/DDSTFactSheet and http://www.nitrc.org/.

extends tools developed in the caBIG®, and the Biomedical Informatics Research Network projects to support national and international collaborations in cardiovascular science. The National Centers for Biomedical Computing are intended to be part of the national infrastructure in Biomedical Informatics and Computational Biology. There are eight Centers that cover biophysical modeling, biomedical ontologies, information integration, tools for gene-phenotype and disease analysis, systems biology, image analysis, and health information modeling and analysis. The centers create 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, providing research training grants to 18 institutions that enroll approximately 200 pre- and post-doctoral trainees each year.

Diagnostic 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 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.

NIH currently funds the Point-of-Care Technologies Research Network, a network of four centers that are developing new point-of-care technologies for early and rapid detection of a wide variety of serious conditions such as neurological emergencies, sexually transmitted diseases, multi-pathogen detection for national disaster preparedness, and diagnosis of infections. These technologies are being designed for use in low-resource settings among underserved populations. The network emphasizes collaboration between front-line health care workers and technology developers so that appropriate tools are created to meet clinical needs.

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. Driving this change will be the use of saliva, an easy-to-access diagnostic fluid that may be useful in the evaluation of oral and systemic diseases, including the identification of HIV, oral cancer, and cardiovascular disease. As envisioned, a drop of saliva will be collected and loaded onto a small, all-in-one device that rapidly measures biomarkers associated with disease allowing early detection, whether in a clinic or in remote resource-poor settings.

Researchers have also been able to detect the inflammatory biomarker C-reactive protein (CRP), a strong predictor of the development of cardiovascular disease, in microscopic quantities of saliva. NIDCR is currently supporting aggressive efforts to provide clinical validation of these experimental results that could provide a self-contained, portable diagnostic test for cardiovascular disease. In related work, salivary biomarkers are being evaluated to detect myocardial infarction in patients presenting with chest pain at emergency departments, providing a tool that may one day enable Emergency Medical Technicians to assess if a patient being transported by ambulance is having a heart attack.

Point-of-care technologies for use in pathology laboratories, emergency rooms, doctors' offices, and homes will be a key component of the evolving health care system. Current devices, developed largely with NIH support, range from handheld glucose monitoring systems used by diabetics to monitor their blood sugar levels to laptop-sized ultrasound scanners. Among the technologies on the horizon is a lens-free optical microscope about the size of a dime. The device could be inserted into a cell phone and used as a diagnostic device in rural settings or developing countries in diagnosing malaria.

Two ultrasound technologies developed with support from NIH are now being used in clinical practice, often outside the hospital or health clinic. The V-Scan is a hand-held ultrasound imaging system the size of a cell phone that is now commercially available through General Electric at a fraction of the cost of traditional ultrasound systems. The device produces high quality images of internal organs in real time and is being used world-wide. Color-coded images enable physicians to quickly identify problems in blood flow or in organs such as the heart. The size and portability of the V-Scan allows diagnosis and treatment to occur at the point of care, whether that is at a patient's bedside or in a remote area.

The second ultrasound technology will be used to treat patients. The High-Intensity Focused Ultrasound is a non-invasive tool that uses a concentrated, highly intense ultrasound beam that can be targeted at a specific area in the body to remove tissue, destroy tumors or repair injured organs or blood vessels. This technique has been approved by the FDA for treatment of uterine fibroids. Studies on other uses such treating brain tumors or for drug delivery to specific organs are continuing.

Another new device has the potential to save eyesight. Developed in collaboration between researchers at NIH and the National Aeronautics and Space Administration (NASA), a dynamic light-scattering probe detects and quantifies a protein in the eye that is critical to keeping the eye's lens clear. Age-related cataracts develop because too little of the protein, alpha crystallin, is present in the eye. The new probe will be used to monitor the effects of cosmic radiation on astronauts' eyes as well as to study the effects of aging on earth-bound eyes. Early detection of alpha crystallin depletion could lead to treatments that could delay or eliminate the need for cataract surgery.

NIH has also partnered with the Department of Biotechnology of the Ministry of Science and Technology in India to support the development of low-cost diagnostic and therapeutic medical technologies that will be used in underserved communities worldwide. One such diagnostic tool under development through NIH support of a small business is a low-cost, simple, and rapid point-of-care test for tuberculosis that will enable rapid diagnosis and ensure that appropriate treatment can be given to all affected individuals, thereby reducing the public health impact of this contagious disease.

Although treatment outcomes for primary cancers have improved in the last decade, many deaths occur as a result of the cancer spreading. Body scans can detect distant cancers but often only after the cancer has begun its destructive work. NIH-supported researchers have created a microchip able to detect circulating tumor cells (CTC) in whole blood. This means that from a sample of a patient's blood the microchip identifies specific cancer cells that are spreading through the body via the circulatory system. Clinicians can then make treatment decisions for specific patients based on the molecular and genomic information provided by the CTC analysis.

NIH also supported two critical phases of the development of a novel "lab-on-a-chip" device for rapidly detecting HIV. The technique has proved highly successful, and the research team has gone on to refine and clinically test this microfluid-based lab-on-a-chip—or mCHIP—in real life settings, with studies demonstrating that the mCHIP can accurately, rapidly, and cost-effectively detect clinically relevant infectious diseases in resource-limited settings.[88]

Another example of "micro" technology improving health care is the portable micro-NMR (nuclear magnetic resonance) device.[89] This device, operated by a smart-phone, is capable of diagnosing tumors from a small sample of cells with greater accuracy than traditional biopsy. The need for a small sample allows the tissue to be obtained using a very thin needle, resulting in reduced pain and recovery time for patients.

Gene Sequencing and Beyond

The sequencing of the human genome in 2003 generated excitement in the scientific community. It gave researchers a new way to analyze the function of cells, tissues, and systems in the body to understand the causes of disease. As more is learned about the genetic contributions to disease, DNA sequence information will become an important tool for individuals and healthcare providers to evaluate individualized disease risk and to improve the prevention, diagnosis, and treatment of disease. However, to deliver genetic information to individuals on a much wider basis, significant decreases must be made in the cost and time needed to sequence an entire human genome. Rapid gains have been made on this front since the start of the Human Genome Project, and costs continue to fall dramatically. NIH supports technology development to make genome sequencing more affordable and genomic information a routine part of health care. For example, NIH-supported researchers are conducting studies to discover the molecular mechanisms underlying complex diseases like addiction, which is strongly influenced by genetics. Investigators studying various neurological and psychiatric illnesses already have linked certain genes with specific diseases using custom screening tools known as "gene chips." Applying these tools to addiction and other brain disorders advances understanding of not only vulnerability to addiction and its co-morbidities, but also of ways to target treatments based on an individual's genetic profile.

[88] Chin CD, et al. *Nat Med*. 2011;17(8): 1015–9. PMID: 21804541.
[89] Haun JB, et al. *Sci Transl Med.* 2011;3(71):71ra16. PMID: 21346169.

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 (IGI)—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 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 magnetic resonance, computed tomography, or ultrasound. 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.

Imaging 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.

More detailed information about the body's internal organs is critical to detecting early stages of disease. Finding new ways of using current MRI systems can advance safer diagnostic methods. In the case of liver disease, biopsies may cause pain, result in missed work, and also carry a risk of bleeding. NIH-supported researchers have developed a non-invasive way to assess the liver using MRI and shear waves, a special type of sound wave. With MRI, the researchers capture snapshots of the shear waves as they propagate through liver tissue. A computer program translates the waves into a map of the liver that displays the stiffness of the organ. Stiffness indicates disease while suppleness indicates healthy tissue. This could provide a safer alternative not only for liver biopsy but also for diagnosis of cancer in the breast, prostate, and kidney.

Harnessing the power of imaging and molecular biology enables us to probe disease mechanisms and image the affected pathways. For example, hyperpolarized C-13 compounds injected into prostate cancer patients can be observed with magnetic resonance spectroscopy as these compounds are

metabolized in cancer cells.[90] These metabolic changes serve as biomarkers for prostate cancer as disease progresses. Decisions on therapeutic management can thus be closely monitored by magnetic resonance spectroscopy.

Recent advances in imaging technology also present opportunities to develop qualified quantitative imaging biomarkers. NIBIB is supporting a public-private consortium called the Quantitative Imaging Biomarkers Alliance (QIBA). This effort aims to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time. QIBA has selected several 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, healthcare professionals and industry.

Investments in 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 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. This is highlighted by the NIH-supported Biomedical Technology Research Centers that develop innovative technologies to aid researchers who are studying virtually every human disease.

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 Research Centers (BTRCs). Supported by NIGMS and NIBIB, there are currently 65 BTRCs nationwide. The technologies developed in the centers involve over 7,000 investigators that are funded by 22 ICs in FY 2010. BTRCs and Biotechnology Resource Centers supported by NIH serve a unique purpose in the broad context of NIH-funded research. They represent a critical mass of technological and intellectual resources with a strong focus on service and training for outside investigators. They develop new technologies and tools in areas including tissue engineering, biomaterials, neural communication technologies, imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, lasers, and BioMEMS (microelectromechanical systems—technology just above nano-size—that manipulate, analyze, and measure biological or chemical materials). Access to these technologies is critical to enabling research, yet they are frequently too advanced or expensive to be widely available. These centers disseminate and promote the application of such cutting-edge technologies. These technologies are developed across the full spectrum from bench to bedside. These centers are multidisciplinary and collaborative and serve as catalysts for integrating the diverse efforts of NIH-supported researchers, and providing technological infrastructure, experimental and computational resources, and expertise.

[90] For more information, see http://www.radiology.ucsf.edu/research/labs/hyperpolarized-mri-tech.

NIH's Biomedical Informatics Research Network is a virtual community of shared informatics resources. The network's grid computing technology 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.

Another technology-intensive collaborative endeavor has developed due to the rapid expansion of the dietary supplement marketplace. This expansion has resulted in a proliferation of ingredients and products. Precise, accurate, and rigorous analytical methods and reference materials are essential for verification of ingredient identity and measuring the amounts of declared ingredients in raw materials and finished products. Also, dietary supplement labels are required to list certain facts about product identity and content and to be truthful and not misleading. That this is not always the case is due, in part, to the lack of proven and agreed-upon methods to precisely assess the quantity of constituents of many supplements and supplement ingredients. NIH's congressionally mandated Analytical Methods and Reference Materials program is intended to assist in providing these critical tools for quality assurance. NIH is partnering with FDA and the National Institute of Standards and Technology (NIST) to promote the development, validation, and dissemination of analytical methods and reference materials for commonly used dietary supplement ingredients.

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 war veterans who have suffered limb damage or loss as well as 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 is especially promising.

NIH and NASA have a strong history of collaboration and share many interests in the life and health sciences. In 2010, NIH awarded the first new grants under the Biomedical Research on the International Space Station (BioMed-ISS) initiative, a collaborative effort between NIH and NASA. Using a special microgravity environment that Earth-based laboratories cannot replicate, researchers will explore

fundamental questions about important health issues, such as how bones and the immune system get weak.

The interplay of ideas among teams of NIH-supported investigators has produced promising techniques to identify mothers at risk for premature delivery. One group used a noninvasive ultrasound approach to assess uterine cervical changes in an animal model weeks before the due date. Another group has developed novel computational tools to analyze uterine biomagnetic signals of term and preterm patients to predict the onset of labor. With an early warning of potential preterm delivery, clinicians may have new tools to fight one of the leading causes of infant death in the U.S.

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, material science, and engineering, NIH is developing a powerful cadre of investigators who will use nanotechnology to significantly change how we diagnose and treat disease. One such group has used electrical forces generated at the molecular level to suspend a microscopic object in mid-air. This finding could contribute to the design of tiny machines to perform surgery. Nanotechnology is also informing new ways of delivering medicine. For example, NIDA-funded researchers have used nanotechnology to successfully demonstrate a prototype programmable skin patch that will let physicians dynamically schedule transdermal medication doses to match a patient's fluctuating needs.

Sharing information across disciplines is critical to nanotechnology research. NIH's Alliance for Nanotechnology in Cancer brings together researchers from biology to oncology. The alliance is building a community of cancer nanotechnologists who develop novel approaches to preventing, diagnosing, and treating cancer and sharing that knowledge with the larger medical community. New nanodevices that quickly and accurately assess proteins and DNA structures implicated in cancer, nanoparticle imaging agents to clearly visualize cancer, and implantable nanosensors to monitor cancer progression will reshape the toolkit clinicians use to fight cancer.

Nanotechnology research is also exploring ways to treat disease. Nanoparticle therapy is a method to deliver the correct amount of a drug to a precise location resulting in more of the drug reaching its target, fewer side effects to healthy tissue and less toxicity to other parts of the body.[91] Natural nanoparticles are also being cultivated from plant viruses as an alternative to manmade nanoparticles for imaging, drug delivery, vaccination, and design of electronic devices. Plant-based particles have advantages over synthetic materials in that they are biodegradable and harmless to humans, have a defined structure so that dyes and targeting tags can be modified and production is inexpensive.[92,93]

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[91] Kolishetti N, et al. *Proc Natl Acad Sci U S A.* 2010;107(42):17939–44. PMID: 20921363.

[92] Steinmetz NF, et al. *Small*. 2011;7(12):1664–72. PMID: 21520408.

[93] Pokorski JK, Steinmetz NF. *Mol Pharm*. 2011;8(1):29–43. PMID: 21047140.

Probing Proteins

Information resulting from the Human Genome Project is now helping scientists as they begin to study more closely the structure of proteins. By visualizing protein structures, researchers gain a better understanding of many of the biochemical processes related to health and disease. This information also can be used to design drugs that target specific parts of a bacteria, virus, or tumor.

Structural biology is a field in which scientists learn about molecules by determining their 3-D structures in atom-by-atom detail. Large user facilities called synchrotrons allow researchers to use X-rays to determine molecular structures more easily, quickly, and cheaply than ever before. NIH funded the development of a new experimental station at the Advanced Photon Source at Argonne National Laboratory. The new station includes three X-ray beamlines for use by scientists from across the U.S. to determine the detailed, three-dimensional structures of molecules, which will lead to improved understanding of basic biological processes and for drug design.

Transforming Health Care

Brain-Computer Interface (BCI) devices are medical devices that operate by exchanging information with nearby portions of brain tissue, which could be placed on the surface of the scalp, near the surface of brain, or penetrate into just the top 2mm layer of tissue. All of these approaches are under consideration as candidate designs for a brain computer interface that could be used to provide a means of "speaking" through a computer. Current development efforts are focused on using the brain signals to support communication through basic, brain-controlled movements. One experimental device has allowed patients to "imagine" movement of fingers to control computer cursor movement across a virtual keyboard and type out messages.[94] Even at this early stage of development, a similar approach might be used to help someone that has been "locked-in" and unable to speak or move limbs as a result of a brainstem stroke, a medical condition that was described in the book, "The Diving Bell and the Butterfly" by Jean-Dominique Bauby.

BCIs are one example of medical implants called neural prosthesis, which are designed to ameliorate the loss of nervous system function resulting from disease or injury. NIH pioneered the development of this technology through more than 35 years of research and development with the goal of helping people with disabilities lead fuller and more productive lives. The program has catalyzed the development of cochlear implants for people with hearing impairments, experimental control of artificial limbs for people with spinal cord injuries, retinal implants that help people regain sight, and deep brain stimulation for Parkinson's disease, among other contributions. Through the years, this program has fostered the development of a robust research community, which now includes private sector companies. The cochlear implant has received the most widespread use, with more than 220,000 users worldwide.

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

[94] Kuiken TA, et al. *JAMA*. 2009;301(6):619–28. PMID: 19211469.

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. NIH supports a number of teams that are developing theranostics that can be applied in clinical studies of human patients.

Chapter 3

Research in Diseases, Disorders, and Health Conditions

Cancer

The Burdens of Cancer and the Necessity and Promise of NIH Research

Although significant progress has been made in reducing the burden of cancer in America, cancer remains a leading cause of death. According to the 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. In that same year, 573,855 people died of some form of cancer[95] and an estimated 1,529,560 individuals were newly diagnosed with cancer.[96] Also in 2010, according to studies by the NCI Surveillance Research Program,[97] medical costs associated with cancer totaled $124.6 billion and are projected to reach at least $158 billion by 2020 (in 2010 dollars).[98] 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 2.6 million because of the growth and aging of the population.

Cancer research funded and conducted by NIH is critical to the national, as well as global, effort to ameliorate and reduce the adverse effects of cancer on the health and lives of cancer patients, their families, and communities, and on the social and economic well-being of institutions, societies, and entire nations. Formidable challenges confront that effort. Cancer itself is not a single disease but is, rather, a complex 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: 1) identifying substances in our environment that we know or suspect will cause cancer; 2) preventing cancer through use of risk assessments based on genetic susceptibilities and environmental exposures; 3) detecting and diagnosing cancer based on knowledge of cancer signaling pathways and biomarkers; 4) predicting cancer progression and outcomes based on examination of the tumor microenvironment and interactions between tumor cells and surrounding, noncancerous cells; 5) developing targeted interventions for

[95] Murphy SL, et al. Table B. Deaths and death rates for 2010 and age-adjusted death rates and percent changes in age-adjusted rates from 2009 to 2010 for the 15 leading causes of death in 2010: United States, final 2009 and preliminary 2010. *National Vital Statistics Reports*; 60(4):31. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf.

[96] Howlader N, et al. SEER Cancer Statistics Review 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD. Available at: http://seer.cancer.gov/csr/1975_2009_pops09/.

[97] For more information, see http://surveillance.cancer.gov/.

[98] Cancer Prevalence and Cost of Care Projections, National Cancer Institute, Bethesda, MD. Available at: http://costprojections.cancer.gov/.

individual cancer patients based on the biology of their individual tumors and predictions of their response to treatment; and 6) 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 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 clinical to translational 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[99] and the Division of Cancer Epidemiology and Genetics[100]—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 and aim to rapidly translate those findings into new preventive and detection methods and therapies. In addition, NCI also 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, and 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, non-communicable diseases, including cancer;
- NCCAM: research on nontraditional approaches to cancer therapies across the cancer continuum;
- NEI: research on cancers of the eye;
- NHGRI: epidemiological and genomic research on cancers;
- NHLBI: research on blood-related cancers; on bone marrow transplantation as treatment for cancers; on COPD and lung cancer; and as the administrative coordinator of the NIH Women's Health Initiative[101], on breast, colorectal, and reproductive cancers;

[99] For more information, see http://ccr.cancer.gov/.
[100] For more information, see http://dceg.cancer.gov/.
[101] For more information, see http://www.nhlbi.nih.gov/whi/.

- NIA: research on the biology of aging as it relates to cancer, such as prostate and skin cancers;
- NIAAA: research on the role of alcohol in colorectal, breast, esophageal, liver, and pancreatic cancers;
- 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 pediatric cancers and breast and reproductive organ cancers;
- NIDA: research on the prevention and treatment of tobacco addiction serving as cancer prevention;
- NIDCD: research on the impact of head and neck cancers on deafness and communication disorders;
- NIDCR: research on head and neck 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, which may increase cancer risk;
- NIEHS: research on the effects of biological, chemical, or physical agents that can lead to cancer; including preparation of the 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;
- NIMHD: research on cancer in diverse populations;
- NINDS: research on brain, spinal cord, and pituitary cancers; and
- NINR: research focused on new initiatives to enable cancer patients and survivors better manage symptoms associated with their cancers and cancer treatments.

NIH Funding for Cancer Research

NIH funding for cancer research was $5,823 million in FY 2010 and $5,488 million in FY 2011 for non-ARRA (regular appropriations) and $803 million in FY 2010 for ARRA appropriations.[102]

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 while 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 can also play a role in initiating molecular aberrations in a cell's genome.

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, understanding the role of altered gene expression in cancer progression, and exploring the roles of susceptibility genes in cancer risk and initiation.

A primary challenge is dissecting the molecular basis of cancer. The Cancer Genome Atlas (TCGA),[103] 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 could also yield information critical to reducing health disparities associated with cancer. In conjunction with the NCI Center to Reduce Cancer Health Disparities,[104] TCGA is working to ensure that adequate numbers of biospecimens are obtained from underserved and underrepresented populations to be

[102] For funding of various Research, Condition, and Disease Categories (RCDC), please see http://report.nih.gov/categorical_spending.aspx.
[103] For more information, see http://cancergenome.nih.gov/.
[104] For more information, see http://crchd.cancer.gov/.

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 non-invasive characterization linked to the cancer genome.

A prime example of TCGA's potential is illustrated by research targeting glioblastoma multiforme, an aggressive form of brain cancer. In the past year, glioblastoma multiforme investigators discovered that about 10 percent of patients with one of the four subtypes of glioblastoma multiforme 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 ovarian cancer offers another illustrative example of the promise of fundamental insight offered by TCGA. Analysis of nearly 500 ovarian cancers through TCGA revealed several tumor subtypes, identified molecular pathways potentially important in tumor maintenance, revealed that mutations in the *TP53* gene are found in virtually all of these cancers, and catalogued the large areas of the genome whose copy number is increased and decreased. The information gleaned from these 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. The TCGA network has selected more than 6,000 gene and microRNA (miRNA) targets for sequencing that represent both protein-coding genes and gene encoding miRNAs.

Many other noteworthy NIH research initiatives are underway to illuminate the mechanisms of cancer. The Therapeutically Applicable Research to Generate Effective Treatments (TARGET)[105] 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. Protein kinase is an enzyme that modifies and functionally changes other proteins. TARGET utilizes high-throughput screening technology to identify the genetic abnormalities in these pediatric cancers, as does another initiative, the Cancer Genome Characterization Initiative.[106] Investigators in the Clinical Proteomic Tumor Analysis Consortium[107] are analyzing the sequences and quantities of proteins in samples collected through TCGA with the goal of comprehensive proteogenomic integration. Proteomics is biological research that combines proteomics (study of proteins) and genomics (study of genomes). Additionally, the Physical Sciences-Oncology Centers[108] program supports innovative ideas that blend perspectives and principles of physical sciences and engineering with cancer biology and clinical oncology with the goal of enhancing the detection and treatment of cancer by increasing understanding of the physical and chemical forces that govern the emergence and behavior of cancer.

[105] For more information, see http://target.cancer.gov/.
[106] For more information, see http://cgap.nci.nih.gov/cgci.html.
[107] For more information, see http://proteomics.cancer.gov/programs/cptacnetwork.
[108] For more information, see http://physics.cancer.gov/centers/.

The Cancer Target Discovery and Development network[109] is accelerating the transition of molecular data to new treatments through gene validation studies as well as 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[110] 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, NIDA, and NCRR, 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.

NCI is conducting GWAS to identify genetic variants associated with cancer risk. The Cancer Genetic Markers of Susceptibility[111] project, originally designed to identify common inherited genetic variations associated with risk for breast and prostate cancer, has grown into a robust research program involving GWAS for a number of cancers (i.e., pancreas, bladder, lung, kidney, brain, esophagus, stomach, testis, non-Hodgkin lymphoma, and osteogenic sarcoma). In addition, NCI's longstanding investment in the follow-up of cancer-prone families has led to new efforts to discover rare gene variants using powerful new advances in whole-exome (the coding regions of the genome that are expressed into proteins) and whole-genome sequencing. 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 those in the private sector through rapid posting to databases.[112] Ultimately, findings from these studies may yield new preventive, diagnostic, and therapeutic interventions for cancer.

Studies through NCI's Cohort Consortium,[113] a large-scale, international collaboration that includes over four million people, are evaluating the role of genetic susceptibility, environmental exposures (including nutrition), and gene-environment interactions for a range of different cancers. In addition, NCI has several ongoing and planned genome-wide association studies to identify genetic determinants of cancer risk, as well as the contributions of major determinants of health such as obesity and tobacco use. NCI has also funded a number of studies through its new Post-Genome Wide Association initiative, the goal of which is to translate GWAS findings into clinical and prevention applications by replicating findings, more accurately pinpointing genomic regions that cause cancer, unraveling the functions of genetic variants, and determining how environmental factors alter genetic risk.

Another major NIH initiative anchored to the goal of clarifying the environmental and genetic risk factors for cancer is the NIEHS-led Sister Study,[114] which focuses on breast cancer. This study involves a

[109] For more information, see http://ocg.cancer.gov/programs/ctdd.asp.
[110] For more information, see http://www.nih.gov/science/models/mouse/resources/hcc.html.
[111] For more information, see http://cgf.nci.nih.gov/resources/cgems.html.
[112] For more information, see http://epi.grants.cancer.gov/dac/ and http://cgems.cancer.gov/data_access.html.
[113] For more information, see http://epi.grants.cancer.gov/Consortia/cohort.html.
[114] For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm.

cohort of 50,000 sisters of women who have been diagnosed with breast cancer. These unaffected sisters are being followed over time, with periodic health updates. The women who develop breast cancer during the follow-up period will be compared with those who remain healthy to identify factors associated with increased cancer risk.

NIH also is supporting a network of Breast Cancer and the Environment Research Programs (BCERPs)[115] to study the impact beginning in the prenatal period through adulthood to determine which environmental exposures may predispose a woman to breast cancer. Initially established in 2003 through a collaboration involving NCI and NIEHS, BCERPs undertake multidisciplinary studies of the genetic, chemical, physical, and social factors that affect breast development during puberty and breast cancer predisposition. An epidemiologic study conducted as part of BCERP is prospectively following through puberty a multiethnic cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a public school population of Caucasian and African American students, to determine how diet influences fat tissue and alter the effects of hormones on sexual maturation. The effects of endocrine disruptors (chemicals that interfere with the hormone system), irradiation, and psychosocial elements also will be studied. 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 exposures to those stressors. Additionally, NIEHS had an ARRA contract to develop communication toolkits targeting parents and health care providers with key messages based on the BCERP research findings.

Other 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[116] is an NIH program focused on expanding our understanding of the role of the microenvironment in which a tumor originates and the critical role it plays during tumor development, progression, 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 linkages 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[117] constitutes a major component of

[115] For more information, see http://www.niehs.nih.gov/research/supported/centers/breast-cancer/index.cfm.
[116] For more information, see http://tmen.nci.nih.gov/.
[117] For more information, see http://ccr.cancer.gov/labs/lab.asp?labid=790.

NIH's inflammation and cancer initiative, which partners expertise in inflammation and immunology with cutting-edge cancer etiology and carcinogenesis research.

Systems biology and systems genetics also are promising 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, 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)[118] to develop a framework for these activities. The ICBP has funded twelve integrative biology centers around the U.S. to provide the nucleus for the design and validation of computational and mathematical models of cancer. Networks of genes can be found and their associations with cancer tested and quantified, and parallel association studies can be conducted in relevant human populations.

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 be responsible for the recurrence of 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.

Basic research is unlocking our understanding of what happens in the cellular microenvironment in and around a developing tumor. One aspect of that research is finding ways to boost the body's own immune responses to cancer that offers 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, and clinical trials using ipilimumab and other anti-CTLA-4 antibodies are underway for some lung and prostate cancers.

Numerous other NCI projects and initiatives are investigating the roles of infectious agents and the immune system in cancer. Current evidence indicates that as many as one in five cancers may have an infectious cause; this number is larger in low and middle-income countries. When infectious causes are discovered, the agent can represent a molecular target for intervention or a biomarker for screening (e.g., human papillomavirus infection of the cervix, hepatitis B and C viruses infection of the liver). NCI-funded investigators are working with U.S. and foreign scientists to study the role of immune dysfunction in the formation of tumors , in part through the study of cancer in HIV-infected individuals, and also by investigating the contributions of chronic inflammation to cancer development. NCI is also actively investigating therapies that utilize host immune cells and responses to combat tumor growth and metastasis. For example, the Center for Excellence in Immunology,[119] an intramural research program, 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

[118] For more information, see http://icbp.nci.nih.gov/.
[119] For more information, see https://ccrod.cancer.gov/confluence/display/COEI/Home.

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 highest resolution.

NCI 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, sedentary behavior, and physical activity. NCI also evaluates mechanisms by which obesity may be related to carcinogenesis using high-throughput technologies such as multiplex assays (an assay that measures multiple analytes in a single cycle), along with other analytic approaches. An example of an initiative in this area is the Transdisciplinary Research on Energetics and Cancer [120] Program, 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.

For reasons that are self-evident, the optimal strategy for individuals, their caregivers, and society at large is to prevent cancer. To this end, NIH research has multiple aims, including modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting cancer process through early medical intervention.

One role of the trans-HHS National Toxicology Program, led by NIEHS, is to review the cumulative state of the science on the potential carcinogenicity of publicly registered substances such as chemicals (e.g. solvents and industrial salts), food additives and herbal medicines (e.g. saccharin, gingko Biloba), and other environmental agents (e.g. asbestos). Determinations are made as to whether a substance is a known human carcinogen or reasonably anticipated to be a carcinogen, as well as other potential toxicities. The findings of these investigations are published in the publically available document, *Report on Carcinogens.* [121]

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 development of a much needed screening assay for this disease, which is currently often detected in late stages. Genomic studies may also identify targets for chemoprevention. The Consortia for Early Phase Prevention Trials[122] involve six major cancer research centers that lead multiple collaborative networks to assess the cancer prevention potential of new agents, with a focus on Phase I and 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, and 3) correlate these effects with clinical endpoints. Continued emphasis will be placed on identifying

[120] For more information, see http://cancercontrol.cancer.gov/trec/.
[121] For more information, see http://ntp.niehs.nih.gov/?objectid=03C9AF75-E1BF-FF40-DBA9EC0928DF8B15.
[122] For more information, see http://prevention.cancer.gov/clinicaltrials/management/consortia.

molecular drug targets, developing successful prevention strategies, and bringing 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®, a 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) now is available. 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 women's lives annually in the U.S. and several hundred thousand more 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 and the mechanisms by which obesity increases the risk of cancer. The initiative is connecting with a number of established initiatives in the areas of diet, physical activity, and weight and is integrated with the *Strategic Plan for NIH Obesity Research.*[123]

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. By the mid-1950s, the mysterious and alarming epidemic in lung cancer, a disease that was almost nonexistent in 1900, was linked to smoking behavior. In the last decade, overall cancer death rates have dropped for the first time in a century, driven largely by the dramatic reduction in male smoking from 47 percent in the 1960s to less than 23 percent today. About 40 percent of this drop in overall cancer rates has been credited to the dramatic reduction in male smoking and male lung cancer deaths since 1991 (more than 146,000 fewer deaths during 1991 to 2003 alone). 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 last 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 non-smokers to environmental tobacco smoke due to recognition of these effects and widespread campaigns to limit or ban smoking in public places. Without these investments, 40 million Americans might still be smoking today, hundreds of thousands of them and those exposed with them would have died prematurely of a tobacco-related disease, and billions of dollars would have been spent on their treatment.

Multiple NIH Institutes have co-funded seven Transdisciplinary Tobacco Use Research Centers,[124] which seek to identify familial, early childhood, and lifetime psychosocial pathways associated with smoking initiation, use, cessation, and patterns of dependence. Research on the genetics of addiction,

[123] Strategic Plan for NIH Obesity Research – A Report of the NIH Obesity Research Task Force (2011). Available at: http://www.obesityresearch.nih.gov/About/StrategicPlanforNIH_Obesity_Research_Full-Report_2011.pdf.
[124] For more information, see http://dccps.nci.nih.gov/tcrb/tturc/.

physiological biomarkers, and advanced imaging techniques should allow the development of individualized and community approaches to the prevention and treatment of tobacco-related diseases. The Transdisciplinary Tobacco Use Research Center model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships. With a special focus on cessation, the NCI-sponsored State and Community Tobacco Control Policy and Media Research initiative will investigate the effectiveness of state and community tobacco control policy and media interventions. Focus areas include secondhand smoke policies, tax and pricing policies, tobacco industry marketing and promotion, mass media countermeasures, and community and social norms.

The NIH-supported Community Clinical Oncology Program (CCOP)[125] provides a network for greater participation in clinical trials on cancer prevention and treatment. There are 48 CCOPs and 16 Minority Based-CCOPs[126] (CCOPs with 30 percent of their new patients from minority populations) currently funded in 35 states and Puerto Rico. The program involves 3,645 physicians participating in 415 hospitals, working on more than 70 active prevention and control trials. The groups responsible for developing and implementing cancer prevention and control clinical trials are known as Research Bases; 13 Cooperative Groups and Cancer Centers have grants to serve as CCOP Research Bases.

The HMO Cancer Research Network (CRN)[127] conducts cancer prevention, early detection, treatment, long-term care, and surveillance research, using data systems of 14 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[128], which has collected data since 1973, regularly samples approximately 26 percent of the U.S. population and has obtained information on 5.7 million cancer cases—380,000 cases are added each year. This database provides critical data on cancer trends and is maintained in collaboration with the CDC's National Center for Health Statistics, the Census Bureau, and the North American Association of Central Cancer Registries.

The National Outreach Network[129] is 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 and also works to enhance recruitment and retention in cancer research.

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.

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[125] For more information, see http://dcp.cancer.gov/programs-resources/programs/ccop.
[126] For more information, see http://ncccp.cancer.gov/Related/MBCCOP.htm.
[127] For more information, see http://crn.cancer.gov/about/.
[128] For more information, see http://seer.cancer.gov/.
[129] For more information, see http://crchd.cancer.gov/inp/non-overview.html.

Molecular profiling is an ongoing effort at NIH, from work at the bench to larger initiatives. In the area of molecular diagnostics, NIH has formed the Early Detection Research Network (EDRN)[130] to bring a collaborative approach to the discovery, development, and validation of early-detection biomarkers for clinical application. Another NIH program, Strategic Partnering to Evaluate Cancer Signatures,[131] 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[132] focuses on determining the gene expression profiles of normal, precancerous, and cancerous cells to improve detection, diagnosis, and treatment. The Cancer Genome Anatomy Project Web site makes tools for genomic analysis available to researchers worldwide.

Yet 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 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 the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate basic science research and the development of clinical applications. The Clinical Proteomic Technologies for Cancer comprises three integrated programs: the Clinical Proteomic Technology Assessment for Cancer network, the Advanced Platforms and Computational Sciences program, and the Proteomic Reagents and Resources Core.

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 United States Prevention Services Task Force, recommend screening for breast, colon, and cervical cancers based on demonstrated mortality reductions in randomized trials (breast and colon cancers) and large population cohort studies (cervical cancer). There is evidence that the process of finding these cancers among the many screened is not optimal. Whereas performance characteristics of individual screening tests (sensitivity, specificity, positive predictive value) are relatively well known, analogous performance characteristics of the entire process remain understudied. To pursue the long-term objective of optimizing the screening processes in community practice, NIH is supporting Population-based Research Optimizing Screening through Personalized Regimens Research Centers.[133] This multi-site, coordinated, transdisciplinary initiative has the scientific goal of supporting research to better understand how to improve the screening process (recruitment, screening, diagnosis, referral for treatment) for breast, colon, and cervical cancer.

As previously noted, efforts at NIH, and at NCI and NIDA in particular, 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, where we have seen steady declines, but

[130] For more information, see http://edrn.nci.nih.gov/.
[131] For more information, see http://www.cancerdiagnosis.nci.nih.gov/scientificPrograms/specs.htm.
[132] For more information, see http://cgap.nci.nih.gov/.
[133] For more information, see http://appliedresearch.cancer.gov/networks/prospr/

now also among 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 concluded National Lung Screening Trial[134] 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 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. The U.S. Preventive Services Task Force has commissioned modeling studies of lung cancer screening by investigators in NCI's Cancer Intervention and Surveillance Modeling Network to fully assess the risks and benefits of screening with low-dose helical computed tomography. 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, colorectal, and cervical cancers; new imaging approaches for more accurate and earlier detection of glioblastoma multiforme, breast, 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 the NIH 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 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.

NIH is working on multiple fronts in the drive to develop new, more effective therapies for cancer. One innovative initiative, the NCI Experimental Therapeutics Program (NExT),[135] 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 adequately addressed by the private sector. NExT is designed to advance clinical practice and bring improved therapies to cancer patients. The discovery engine of this program is the Chemical Biology Consortium.[136] The 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. Additionally, the highly successful Developmental Therapeutic Program provides the resources needed to facilitate discovery and late-stage preclinical development through the final steps of development to first-in-human studies. Concurrent molecular imaging and/or

[134] For more information, see http://www.cancer.gov/clinicaltrials/noteworthy-trials/nlst.
[135] For more information, see http://next.cancer.gov/.
[136] For more information, see http://next.cancer.gov/discoveryResources/cbc.htm.

pharmacodynamic assay development provided by the Cancer Imaging Program,[137] National Clinical Target Validation Laboratory,[138] and CCR allow early assessment of potential clinical biomarkers. These coordinated and focused 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[139] has been 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. In support of the NExT initiative, the Center for Advanced Preclinical Research[140] will accelerate development of therapeutics and diagnostics for human diseases by providing state-of-the-art animal models for preclinical studies that are genetically programmed to develop diseases in the same way they arise in humans.

Another program, the Cancer and Inflammation Program,[141] supports cancer-related basic, translational, and clinical research in imaging sciences. Program initiatives include the development and delivery of image-dependent interventions for malignant and premalignant conditions; standardized models for the design of clinical trials that use imaging technologies; development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and development of imaging methods for cancer detection and treatment and for monitoring responses to therapy.

NCI investments in basic research lead to 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 have been recently 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[142] 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, the Comparative Oncology Program has established a multicenter collaborative network of extramural comparative oncology programs to design and implement preclinical trials involving domesticated animals.

[137] For more information, see http://next.cancer.gov/pdResources/imaging.htm.
[138] For more information, see http://next.cancer.gov/pdResources/pharmacodynamics.htm.
[139] For more information, see http://cadp.cancer.gov/.
[140] For more information, see http://atp.ncifcrf.gov/atpi/ppt/capr.
[141] For more information, see http://imaging.cancer.gov/.
[142] For more information, see https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Home.

Using genomics to match drugs to the patients most likely to benefit from them, and conversely sparing patients courses of treatment from which they will not benefit, promises to be among the new modalities for successfully managing cancer. The potential therapeutic impact of basic discoveries made by TCGA and other efforts in cancer genomics has been dramatically illustrated within the past year by the development of effective drugs against metastatic melanoma. In 2003, studies of cancer genomes uncovered a common mutation in BRAF, a gene that encodes a protein known as B-raf. Early stage clinical trials at NCI-designated Cancer Centers of drugs targeted against the mutant BRAF enzyme showed that most melanomas with the relevant mutation regressed dramatically.[143] Although tumor regression generally lasted less than a year, NCI-supported investigators have already pinpointed the cause of resistance to BRAF inhibitors, outlining a pathway to more sustained control of this lethal disease.[144] A Phase III clinical trial is currently underway targeting ALK mutations in lung cancer.[145] Such targeted treatments, made possible by deeper understanding of the genetic and molecular workings of cancer cells, can only be pursued with robust and sustained support both for fundamental research and for faster integration of research into clinical applications to improve patient outcomes.

The emerging scientific landscape of precision medicine made possible by genomic information about cancer offers the promise of significant advances for current and future cancer patients. This effort is complemented at NCI by a new initiative to engage investigators with novel ideas. A funding opportunity announcement (Request for Applications) was released in the fall of 2011 soliciting research applications to address NCI's 24 Provocative Questions[146]—important but non-obvious questions that will stimulate NCI's research communities to use laboratory, clinical, and population sciences in especially effective and imaginative ways. The potentially game-changing answers to these scientific questions could influence the directions taken by NCI-sponsored research in the future, and could contribute to an even greater wave of discovery and progress against cancer.

The Repository of Molecular Brain Neoplasia Data (REMBRANDT)[147] 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. The Trial Assigning Individualized Options for Treatment, or TAILORx,[148] is examining the possibility that a molecular profiling test that examines many genes simultaneously can help predict whether women with early-stage breast cancer would benefit from chemotherapy in addition to radiation and hormonal therapy. Incorporation of molecular data into clinical decision making could spare some women unnecessary treatment if chemotherapy is not likely to impart substantial benefit. The new Provocative Questions initiative may facilitate identification of molecular targets and markers for testing in future clinical trials by promoting research to identify the genetic and epigenetic changes that are most critical to the

[143] For more information, see http://www.cancer.gov/ncicancerbulletin/061411/page2.
[144] For more information, see http://www.cancer.gov/ncicancerbulletin/112911/page2.
[145] For more information, see http://www.cancer.gov/ncicancerbulletin/090611/page2.
[146] For more information, see http://provocativequestions.nci.nih.gov/.
[147] For more information, see https://caintegrator.nci.nih.gov/rembrandt/.
[148] For more information, see http://www.cancer.gov/clinicaltrials/noteworthy-trials/tailorx.

maintenance of oncogenesis as well as the properties of nonmalignant lesions that predict the likelihood of progression to invasive or metastatic disease.

In order to facilitate the translation of molecular therapeutic approaches to clinical use in the context of radiotherapy, the Radiation Research Program[149] tests NCI-developed drugs for their efficacy as radiosensitizers under a variety of *in vitro* environmental conditions and carries out *in vivo* radiation response studies. The program also fills an essential role by coordinating the transfer of NCI-developed drugs to extramural and foreign investigators interested in radiation studies, while avoiding duplication of effort between research groups. Efforts are underway to rescue chemotherapeutic drugs abandoned due to systemic toxicity and to formulate efficient platforms for gene specific short-interfering RNA (siRNA) delivery using nanotechnology-based constructs.

Innovative research in genetics, imaging, and cancer molecular signatures is laying the groundwork for customized cancer patient care. The Advanced Technology Program[150] 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[151] 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. Researchers funded through the Quantitative Imaging Network[152] are developing and validating quantitative imaging methods and software tools for the measurement of response to drug or radiation therapy for use in clinical trials.

Clinical trials are a critical step in moving potential therapies into clinical practice. NCI supports clinical trials through a number of mechanisms, including the Cooperative Group Program, which is 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.[153] The Cooperative Groups are now being reorganized to streamline the development and execution of trials, to select and prioritize trials through stringent peer review, and to fully fund the most promising and innovative studies. In an effort to maximize molecular characterization of cancers, biological specimens from trial participants will be collected for future research. Other trials are conducted within the intramural research program and with extramural support of investigator-initiated projects. NCI has also implemented the Biomarker, Imaging, and Quality of Life Studies Funding Program,[154] which supports promising correlative studies related to biomarkers, imaging, and patient quality of life, in association with Phase III and large Phase II trials. In order to facilitate management and coordination of the clinical trials portfolio, NCI is creating

[149] For more information, see http://rrp.cancer.gov/.
[150] For more information, see http://atp.ncifcrf.gov/.
[151] For more information, see http://www.cc.nih.gov/centerio/index.html.
[152] For more information, see https://wiki.nci.nih.gov/display/CIP/QIN.
[153] For more information, see http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group.
[154] For more information, see http://bigsfp.cancer.gov/.

the Clinical Trials Reporting Program,[155] a comprehensive database that will contain regularly updated information on all interventional trials.

NCI also encourages both intramural and extramural collaborations as part of its effort to develop new treatments for cancer. One example involves the drug rapamycin, which specifically and potently acts upon an essential signaling pathway in head and neck squamous cell carcinoma, the most common of the head and neck cancers. As part of an international initiative headed by NIDCR, scientists collected hundreds of head and neck cancer tissues from all over the world.[156] Examinations of the collected tissues confirmed that the mammalian target of rapamycin is a good target for treating head and neck cancer. Such findings led scientists to develop novel mouse models to test the impact of rapamycin administration on head and neck cancer, which was remarkable. Rapamycin caused the regression of established cancer lesions and prevented the development of new ones from pre-malignant lesions. New evidence in animal models suggests that rapamycin may also halt the spread of head and neck cancer to other parts of the body. In collaboration with NCI, NIDCR investigators have begun a clinical trial to evaluate the possible survival benefits of treating head and neck cancer patients with rapamycin before surgical removal of their tumors. These studies may lead to improvement in the overall five-year survival rate for head and neck cancer, which has remained constant at 50 percent for more than three decades. Melding basic science breakthroughs with decades of existing clinical data on rapamycin administration, this clinical trial could clear the way for more targeted and effective treatment of head and neck cancer patients.

Research on the quality of cancer care is essential to ensure the best outcomes for all who may be affected by cancer. Research in this area 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 themselves at increased risk for cancer due to shared cancer-causing genes, lifestyles, or environmental exposures. Dissemination of research helps ensure that the knowledge gained through NIH-supported research is appropriately and effectively communicated to health care providers, policymakers, and the public.

The Cancer Intervention and Surveillance Modeling Network[157] is a consortium of NCI-sponsored investigators that seeks to improve our understanding of the impact of cancer control interventions (e.g., prevention, screening, and treatment) on population trends in incidence and mortality using statistical modeling. The network is focused on meeting the expanding scientific need for tools which assist in synthesizing emerging evidence in a timely manner due to the extraordinary pace of developments in cancer control technologies, basic science studies investigating molecular and biological determinants of cancer risk, upcoming results from clinical trials, and new health-related data.

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:

[155] For more information, see http://www.cancer.gov/clinicaltrials/conducting/ncictrp/main.
[156] Molinolo AA, et al. *Clin Cancer Res*. 2007;13(17):4964-73. PMID: 17785546.
[157] For more information, see http://cisnet.cancer.gov/

- The Quality of Cancer Care Committee[158] is an interagency working committee that has fostered collaborative projects directly involving HRSA, AHRQ, CMS, Department of Veterans Affairs, IHS, 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[159] and the Cancer Care Outcomes Research and Surveillance Consortium;[160]

- Studies on improving the quality of cancer communications; and

- Research to monitor patterns of treatment dissemination and quality of care through Patterns of Care/Quality of Care Studies.[161] In addition, the NCI Community Cancer Centers Program[162] is researching how best to bring effective cancer treatments to patients in the communities where they live.

Thanks in large part to the success of new treatment strategies, the population of cancer patients surviving more than five years from diagnosis continues to grow. NIH supports research and education efforts aimed at professionals who care for cancer patients and survivors. The Office of Cancer Survivorship[163] addresses the physical, psychosocial, and economic impacts of cancer diagnosis and its treatment and 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.

To improve the outcomes of cancer patients, advances in knowledge must be effectively disseminated to the public and health care providers. The Cancer Control P.L.A.N.E.T.[164] 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 accessing products and guidelines for planning and evaluation.

Due in part to an explosion of information through any 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

[158] For more information, see http://outcomes.cancer.gov/networks/qccc/.
[159] For more information, see http://outcomes.cancer.gov/areas/assessment/comwg.html.
[160] For more information, see http://outcomes.cancer.gov/cancors/.
[161] For more information, see http://healthservices.cancer.gov/surveys/poc/.
[162] For more information, see http://ncccp.cancer.gov/.
[163] For more information, see http://dccps.nci.nih.gov/ocs/office-survivorship.html.
[164] For more information, see http://cancercontrolplanet.cancer.gov/.

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,[165] which is a national survey uniquely dedicated to learning how people find, use, and understand health information. Survey researchers examine how different communication channels are used by adults 18 years and older, including the Internet, 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 has made significant progress in expanding access to clinical trials for patients in community settings and for minority and underserved populations. Representing 340 hospitals and 2,900 physicians, the CCOPs enroll one-third of all participants in NCI cancer prevention, control and treatment trials nationwide. The current 16 Minority-Based CCOPs, comprising 55 hospitals and 475 physicians, and including 100 minority investigators, enroll patients into approved trials in areas with at least 30 percent underserved or minority populations. Minority-Based CCOPs have an average of 64 percent minority participants on trials at their sites. The NCI Community Cancer Center Programs was expanded from the original 16 pilot sites to a total of 30 sites with the goal of improving the quality of cancer care for more than 50,000 new cancer patients from rural, inner-city, and underserved communities each year and providing them the opportunity to participate in cancer research.

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[166] program 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[167] 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 is also 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.

[165] For more information, see http://hints.cancer.gov/
[166] For more information, see http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html.
[167] For more information, see http://crchd.cancer.gov/inp/gmap-overview.html.

The incidence of cancer in low and middle income countries is projected to increase in the coming years. It is estimated that approximately 70 percent of cancer deaths will occur in low and middle income countries. High prevalence of cancer risk factors such as smoking, unhealthy diet, and infections are attributable 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[168] 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 United States and other countries through training and education as well as research cooperation with other countries. The Center has offices in other countries, including India, China, and Belgium, and has established research networks in Latin America, the Caribbean, and Ireland.

The infrastructure required for initiating and sustaining a robust, multi-front 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.

The Cancer Biomedical Informatics Grid® (caBIG®)[169] is an important initiative designed to accelerate research discoveries and improve patient outcomes by supporting the sharing of data and tools among researchers, physicians, and patients throughout the cancer community. caBIG® has developed and freely distributed more than 40 software tools with applications in basic and clinical research on cancer and other diseases. NIH is committed to extending caBIG® across the broader cancer research and care community. More than 1,500 individuals, representing more than 450 organizations in 13 countries, have so far participated in caBIG® projects. caBIG® technologies have been used to link the 66 Cancer Centers, NCI Community Cancer Centers Program, TCGA, other NIH Institutes, FDA, and international partners.

The new BIG Health Consortium™ is a public-private partnership among key stakeholders in health care including patient advocates, health care providers, payers, product innovators, investors, and information technologists. Its mission is to show how and why personalized medicine works. Through a series of demonstration projects, BIG Health™ will model a new approach in which clinical care, clinical research, and scientific discovery are linked. The key enabler for this linkage is the informatics infrastructure that NIH has already developed—caBIG®.

The Alliance for Nanotechnology in Cancer, a comprehensive endeavor involving both public and private sectors, is designed to accelerate the application of nanotechnology to cancer research. This initiative supports research on novel nanodevices to detect and pinpoint the location of cancer at its earliest

[168] For more information, see http://www.cancer.gov/aboutnci/globalhealth.
[169] For more information, see https://cabig.nci.nih.gov/.

stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective in killing those cells. Programs of the Alliance include the Nanotechnology Characterization Laboratory; Cancer Nanotechnology Platform Partnerships; Centers of Cancer Nanotechnology Excellence; Innovative Technologies for Molecular Analysis of Cancer; and Tumor Stem Cells in Cancer Biology, Prevention, and Therapy.

Given the global burden of cancer and opportunities to identify new approaches in prevention and treatment through international collaborative research, NIH is strengthening health research infrastructure and building global research capacity through the International Tobacco and Health Research and Capacity Building Program. 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 nations where tobacco consumption is a current or anticipated public health problem. Because the overwhelming majority of smokers begin tobacco use before they reach adulthood, the program emphasizes research on determinants of youth smoking in diverse cultural and economic settings, as well as effective ways to prevent young people from starting to smoke.

A cornerstone of the infrastructure for NIH-sponsored cancer research is the 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. Specialized Programs of Research Excellence (SPORE) grants, each of which focuses on a specific organ site, such as breast or lung cancer, or a group of highly related cancers, such as gastrointestinal cancers, involve both basic and clinical/applied scientists (team science) and support projects that will result in new approaches to prevent, detect, diagnose, and treat human cancers.

The 66 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 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 both quality of the imaging and shortened time to clinical trial initiation can be assured.

The SPOREs foster bi-directional translational research by supporting multi-project, interdisciplinary, and in some cases, multi-institutional research that will result in diverse new approaches to the prevention, early detection, diagnosis and treatment of human cancers. SPOREs create an environment for inter-SPORE collaboration and collaboration with other government and non-governmental groups to increase cross-fertilization of ideas, leverage resources, to reduce duplication and to ensure access of resources to scientific community ultimately facilitating the movement of SPORE research along the translational science continuum. SPOREs encourage 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 NCI Cooperative Groups or industrial partners for evaluation in later stage clinical trials. SPOREs also support novel 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, to extend survival, and to increase the quality of life of cancer patients.

Research workforce development is critical to maintaining and enhancing the nationwide (as well as global) infrastructure for cancer research. NCI, in particular, is committed to cultivating and supporting a cadre of researchers that span the career continuum; gaps at any stage of this continuum will compromise the quality of cancer research. NCI is investing in early-stage investigators to attract talent and ensure the future of cancer research and is also supporting established investigators who have proven their ability to conduct robust science and who provide mentoring for the next generation of researchers. NCI supports training within the intramural research program 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 Ruth L. Kirschstein National Research Service Award (NRSA) training program. NCI-awarded NRSAs support the training and mentoring of predoctoral and M.D./Ph.D. or other dual-degree students in laboratory and/or clinical research, helping them to become productive, independent research investigators and clinician-scientists.

NCI also supports training in a number of other disciplines. The Physical Science-Oncology Centers program trains undergraduate, graduate, and postdoctoral trainees with the aim of cultivating a workforce capable of working at the interface of the physical sciences and cancer biology. Additionally, the Basic Behavioral and Social Science Opportunity Network (OppNet) offers educational activities and short-term career development experience to encourage new and established investigators to engage in basic behavioral and social science 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. Finally, NCI also offers support to investigators interested in translational and clinical research. The SPORE Career Development Programs support investigators who wish 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 initiative, 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

Composed of the brain, spinal cord, sensory organs, and nerves of the body, the nervous system underlies perception, movement, emotions, learning, and memory, and 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 due to injury or infection, and its repair mechanisms are poorly understood. Neuroscience research seeks to understand the nervous system and its functions in health and disease. Given its intrinsic complexity and central role in physiology and behavior, this understanding must necessarily come from multiple perspectives. Accordingly, neuroscience research spans many disciplines, from genetics to physiology to psychology, and applies tools from areas such as molecular biology, anatomy, computer science, and imaging technologies.

Neuroscience is a unifying theme in NIH research. 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, 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.

The principal aim of NIH research in neuroscience is to reduce the burden of diseases that affect the nervous system, including 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. Whether led by single investigators or conducted through centers and consortia, NIH neuroscience research includes basic science studies of normal function and development in both humans and animal models, translational research that develops medications or other therapies, and clinical trials that test interventions in patients.

Nervous system disorders include common killers and major causes of disability like stroke, multiple sclerosis, and epilepsy, as well as hundreds of less common diseases, such as lysosomal storage disorders, spinal muscular atrophy, muscular dystrophies, inherited neuropathies, neurofibromatosis, tuberous sclerosis, and Rett and Tourette syndromes. 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, glaucoma, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). Still others are known or suspected of resulting from environmental exposure to substances, such as pesticides, solvents, PCBs, and metals. 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. This research also aims to understand the multiple aspects of the nervous system that disease can affect and has shared support across NIH for basic science studies of the cerebral vasculature, electrochemical signaling in neurons and other cells, mechanisms of development and cell death, neuromuscular function and motor control, and behavior and cognition. In addition, NIH works to enhance the lives of those disabled by stroke, traumatic brain injury, spinal cord injury, and other neurological conditions through research supported by NICHD's National Center for Medical Rehabilitation Research and other ICs on neuroplasticity, recovery and repair of motor and cognitive function, and rehabilitative and assistive strategies and devices.

Brain disorders affecting cognitive, emotional, and behavioral function include schizophrenia and psychoses; autism spectrum disorder and other developmental disorders; mood and anxiety disorders; addiction to nicotine, alcohol, and other substances; and post-traumatic stress disorder, eating disorders, attention deficit hyperactivity disorder (ADHD), and others. Through research efforts led by NIAAA, NIDA, NIMH, NIEHS, 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 abused substances on the nervous system) so as to develop effective therapies and interventions for treatment and prevention.

Communication disorders 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. One such disorder, aphasia, results from damage to portions of the brain that are responsible for language. This disorder usually occurs suddenly, often as the result of a stroke or head injury, but it 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 this disorder. The goal of this research is to develop therapies to improve an individual's ability to communicate by helping the person use remaining abilities, to restore language abilities as much as possible, to compensate for language problems, and to learn other methods of communicating.

Sight, smell, hearing and balance, and our other primary senses, require specialized nerve cells that respond to specific features of the external or internal environment and send signals to the brain. For example, light coming through the lens of the eye projects onto photoreceptor neurons in the retina. Absorption of light causes the protein structure within these cells to twist, triggering a cascade of molecular and electrical changes in the photoreceptor cell, which then send signals to the brain for further processing. 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 disorders of human communication.

Although vital to survival, the sensation of pain also is symptomatic of many diseases with origins in and outside the nervous system, such as migraine and other headaches and cancer-related pain. NIH pain research is led by NINDS and the NIH Pain Consortium, which coordinates research across NIH in this

area with the guidance of an Executive Committee comprised of the NINDS, NIDCR, NINR, NCCAM, and NIDA Directors.

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 and NIDDK, focuses on areas such as circadian rhythms and sleep disorders; neuroendocrine processes that regulate stress responses, 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, and associated conditions such as hydrocephalus, cerebral palsy, Down syndrome, and other causes of intellectual and learning disabilities. Nervous system development continues into early adulthood in humans, 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, NIH research on the aging nervous system includes studies of age-related disorders such as Alzheimer's disease (AD) and other dementias, as well as environmental and lifestyle factors affecting neurological, cognitive, and emotional health in aging populations.

Across all ages, the nervous system is a common target of exposure to toxins, pollutants, metals, food constituents, 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.

NIH also considers diseases of the nervous system from a global point of view. Coordinated in part by FIC, NIH supports neuroscience-related research around the world in unique populations and environments and on factors contributing to disparities in disease vulnerability and treatment quality and access, such as socioeconomic conditions and infectious disease.

Nervous system disorders 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.[170] In the U.S., stroke is the fourth leading killer of adults and results in annual medical and disability costs totaling more than $34 billion and estimated to reach almost $96 billion by 2030.[171] Each year, another 1.7 million Americans sustain traumatic brain injury (TBI), the leading cause of death and long-term disability in young adults,[172] with direct and

[170] For more information, see http://www.who.int/mediacentre/news/releases/2007/pr04/en/index.html.
[171] Roger V, et al. *Circulation.* 2012; 125(1):e2–e220. PMID: 22179539. Heidenreich PA, et al. *Circulation*. 2011; 123(8)933–44. PMID: 21262990.
[172] For more information, see http://www.cdc.gov/traumaticbraininjury/statistics.html.

indirect costs reaching approximately $76.5 billion in 2000.[173] 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.[174] According to the Department of Veterans Affairs, tinnitus (ringing in the ears) is the most prevalent service-connected disability of American veterans, with more than 744,000 veterans receiving disability compensation for tinnitus as of the end of FY 2010.

In a given year, approximately 12.5 million American adults (or one in every 17) suffer a debilitating mental illness.[175] Mental disorders result in more disability for U.S. adults than any other class of medical illness,[176] and a conservative estimate places the total direct and indirect annual costs of mental illness at more than $300 billion.[177] In 2011, among persons in the U.S. ages 12 years or older, 16.7 million were classified with dependence on or abuse of alcohol, and 6.5 million with dependence on or abuse of illicit drugs.[178] 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.[179]

Mental illness and neurological disorders affect people of all ages. An estimated 17 percent of U.S. children have a developmental or behavioral disorder such as autism spectrum disorder, intellectual disability, or ADHD.[180] Current demographic trends project a growing burden from age-related diseases of the nervous system as populations benefit from increased longevity. One in seven U.S. adults ages 72 years and older has dementia, and estimates of the prevalence of Alzheimer's disease range from 2.4 million to 5.1 million, a number expected to rise to as many as 13.2 million by 2050 unless effective interventions are developed.[181]

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[180] U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. The National Survey of Children with Special Health Care Needs Chartbook 2001. Rockville, MD, 2004. For more information, see http://mchb.hrsa.gov/chscn/.

[181] Plassman BL, et al. *Neuroepidemiology*. 2007;29:125–32. PMID: 17975326. Hebert LE, et al. *Arch Neurol.* 2003;60:1119–22. PMID: 12925369.

NIH Funding for Neuroscience and Disorders of the Nervous System

NIH funding for research in neuroscience and disorders of the nervous system was $5,515 million in FY 2010, and $5,548 million in FY 2011 for non-ARRA (regular appropriations) and $794 million in FY2010 for ARRA appropriations.[182]

Summary of NIH Activities

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

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.

During early human embryonic development, a flat surface of cells destined to become the brain and spinal cord rolls into a structure called the neural tube. Defects resulting from improper neural tube formation, including spina bifida and anencephaly, are among the most common birth defects. A randomized clinical trial supported by NICHD recently showed that prenatal fetal surgery to repair the spinal opening in the most common form of spina bifida resulted in improved outcomes as compared to standard postnatal surgery.[183] NICHD and NINDS are supporting a follow up study to determine the effects of prenatal repair on adaptive behavior, cognitive and motor function, brain morphology and microstructure, urologic health, and other outcomes at school age. Other NIH-funded studies explore the developmental mechanisms of neural tube closure, including structural, genetic, and dietary influences in animal models and in humans, which may identify targets for intervention or prevention.

NINDS also supports a broad portfolio of research on hydrocephalus, a condition that often develops in people with spina bifida and other developmental brain malformations. Shunts to drain excess cerebrospinal fluid are the most common treatment for hydrocephalus, but they often fail due to blockage or infection. In 2009, NINDS and NICHD issued a funding opportunity announcement for small business research to improve the design, operation, and monitoring of CSF shunts. The initiative brought

[182] For funding of various Research, Condition, and Disease Categories (RCDC), see http://report.nih.gov/categorical_spending.aspx.
[183] Adzick NS, et al. *NEJM*. 2011;364(11):993–1004. PMID: 21306277.

increased small business attention to this applied research need, and the awards made so far are supporting the development of implantable and non-invasive diagnostic and monitoring devices, novel materials for preventing shunt infection and blockage, and a new shunt design with feedback control.

Developmental disability is a severe, long-term disability that can affect cognitive ability, physical functioning, or both. According to the CDC, there are an estimated 35–43 million people with physical and mental disabilities in the U.S. 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 autism spectrum disorder; and research programs in genetic/genomic disorders, inborn errors of metabolism, and mitochondrial disorders. In addition, NIH is supporting the development of new technologies for newborn screening and an infrastructure to promote 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.

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, Parkinson's disease, depression and other mood and anxiety disorders, addiction, and autism spectrum disorder. NIAAA- and NIDA-supported researchers examined the role that variability in genes that encode a specific receptor for the neurotransmitter (neurotransmitters are chemicals involved in transmitting signals from one nerve cell to another) dopamine may play in improving outcomes of a substance use prevention intervention in a case control study of African American rural adolescents. The study, which focused on parenting behavior, found that youth carrying one variation of this gene (DRD4) not only were more responsive to the intervention than youth with another variation, but also that they reduced past month alcohol or marijuana use over a 29-month period. Taken together with the previous finding that variation in a gene that regulates the actions of the neurotransmitter serotonin influences initiation of adolescent substance use, the results suggest different genes may influence different phases of substance use and highlights potential opportunities to match individuals to prevention programs based on genotype.

NIH supports broad efforts to understand how autism spectrum disorder may arise from combined effects of genetic vulnerabilities and exposure to potentially harmful environmental agents during key periods of development. Recent research suggests that environmental factors may play a much greater role in autism risk than previously suspected and could even be more influential than genetic factors. These findings stem from a study in twins[184] designed to model the genetic and environmental factors that contribute to the development of autism. Using mathematical modeling, the researchers propose that environmental factors accounted for 55 percent of autism risk, while genetic heritability contributed less than 40 percent. The difference in rates among fraternal twins and siblings, who share

[184] Hallmayer J, et al. *Arch Gen Psychiatry*. 2011;68(11):1095–102. PMID: 21727249.

similar amounts of DNA, suggests that environmental factors in the womb may be an important area of future study.

Although all forms of autism spectrum disorder are characterized by challenges in three core domains of functioning (social impairments; communication difficulties; and restricted, repetitive, or stereotyped patterns of behavior), considerable heterogeneity exists across individuals with autism spectrum disorder in these and other clinical features, suggesting the contribution of multiple developmental trajectories and causal factors. One cross-cutting theme highlighted in the Interagency Autism Coordinating Committee's (IACC) Strategic Plan for autism spectrum disorder research is the need to understand this heterogeneity, which could lead to new insights into the causes of autism spectrum disorder, improved diagnosis, and more targeted intervention strategies. To examine the genetic basis of autism, researchers sequenced the protein-coding region of the genome (called exome) of 20 people with autism and their parents, and identified 21 spontaneous or *de novo* mutations.[185] Of the 21 mutations, four were determined to be potentially causative (*FOXP1*, *GRIN2B*, *SCN1A*, and *LAMC3*). Three of the four genes identified in the study had previously been associated with autism, intellectual disability without autism, and epilepsy. The fourth mutation, *LAMC3*, had never before been linked to autism and represents a potential new avenue of research. Furthermore, within the study, two of the four children had been hit with a "genetic double-whammy"—both inheriting a harmful gene mutation from their parents and having a *de novo* mutation. These two cases support the "multi-hit" theory of autism—that a combination of mutations in the same pathway is necessary to cause severe autism or related disorders. The authors note that the study supports the role of *de novo* mutations as a major genetic contributor to autism.

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. In the NIH Magnetic Resonance Imaging (MRI) Study of Normal Brain Development, NIH-supported researchers at seven collaborating institutions collected brain scans and clinical and behavioral data from more than 500 healthy infants, children, and adolescents over the course of seven years, providing important baseline information that could identify signs of atypical brain development. The data gathered and analytical tools developed for this longitudinal study are available to the broader research community in an online, searchable database. An improved understanding of the normal course of human brain development also is yielding insights into behavioral and cognitive development and function across the lifespan. For example, previous brain 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; however, it is unclear whether the structural and functional deficits that were observed predated the onset of alcohol use or occurred as a consequence. To further elucidate how alcohol impacts the developing adolescent brain in both the short and long term, NIAAA is supporting multisite longitudinal studies of youth ages 12–21, capturing them before they begin to drink. The studies are

[185] O'Roak BJ, et al. *Nat. Genet*. 2012;44(4):471. PMID: 21572417.

using advanced neuroimaging technology as well as neuropsychological and behavioral measures to assess alcohol's effects on brain development and the associated cognitive, affective and behavioral processes.

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 other related risk behaviors, as well. The NIH Underage Drinking Initiative similarly supports research on prevention of underage drinking and its risk factors, as well as efforts to develop and implement effective interventions within a developmental framework.

Neuroplasticity: Substrates for Change and Repair

Throughout development, and even once its 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.

One project funded by NEI provides a unique opportunity to study neuroplasticity and visual processing while also providing humanitarian benefit. Project Prakash operates in India, which has the largest population of blind children, many of whom live in poor, remote villages with limited access to professional eye care. The project screens thousands of children for treatable conditions, such as dense congenital cataracts that are routinely removed in the U.S. and has provided vision to hundreds. The treated children are old enough to describe the objects they are beginning to see and learning to recognize after gaining sight. Using behavioral tests and neuroimaging to study how the brain turns visual input into recognizable images, the results have provided remarkable insights. For example, contrary to previous theories, Project Prakash is showing that even after years of being blind since birth, children can still acquire complex visual abilities, providing hope for restoring functional vision to many children.

However, neuroplasticity also can 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 like 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 the case of drugs of abuse and levodopa-induced

uncontrolled movements (dyskinesias) in Parkinsonian patients. By better understanding the underlying mechanisms of neuroplastic changes in the nervous system, researchers may be able to both 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 infection and inflammation. In 2010 and 2011, NINDS announced several new initiatives that aim to better understand the causes of epilepsy and to develop new ways to treat or prevent its development in those at risk.

- The Epilepsy Centers without Walls program supports multidisciplinary consortia to solve specific challenges in the prevention, diagnosis, or treatment of epilepsy. Although causal genes have been identified for a number of rare, familial epilepsy syndromes, the genetic contributors to more common forms of epilepsy are not well known, and the first awarded Center aims to identify new genes and genetic pathways by analyzing 4000 genomes of epilepsy patients and families collected by several major research groups. NINDS is also supporting planning grants in advance of a potential Center without Walls focused on Sudden Unexplained Death in Epilepsy and has announced a new funding opportunity for planning a Center focused on treatments to prevent epilepsy or modify the course of disease.[186]

- The Cooperative agreement program for epilepsy therapy development supports translational research to develop new ways to treat or prevent epilepsy, with a goal for successful projects to result in Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications to the FDA. NINDS supports a project through this program to develop a seizure prediction and drug delivery system that will administer antiepileptic drugs only at times of high seizure likelihood. Such intelligent drug delivery may not only prevent seizures, but could also limit adverse cognitive and physical side effects associated with chronic antiepileptic drug exposure.[187]

- The Epilepsy EUREKA program encourages innovative and transformative epilepsy research to uncover disease mechanisms. NINDS has made 11 awards through this program, each of which employs the latest research methods to provide new insights into understanding and ultimately treating epilepsy.[188]

Mental and addictive disorders are known to have a strong neurodevelopmental component and are associated with functional changes in highly plastic brain areas, such as the prefrontal cortex, which play a key role in cognition and impulse control. Recent studies suggest that putative schizophrenia risk genes are involved in regulating neuroplasticity, and alterations in their expression and function may contribute to the abnormal pattern of cortical connectivity observed in schizophrenia.

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[186] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-11-007.html and http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-11-006.html.
[187] For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-10-144.html and http://grants1.nih.gov/grants/guide/pa-files/PAR-10-143.html.
[188] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-12-005.html and http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-11-003.html.

NIH will continue to support research on treatments for mood disorders through clinical trial networks and the Innovative Approaches to Personalizing the Treatment of Depression Program. Ongoing studies include investigations on susceptibility genes and associations with brain structural changes in major depressive disorders; analysis of biomarker predictions of outcome based on quantitative electroencephalographic features that change during a week of exposure to antidepressant medications; and observational studies using longitudinal data from large population-based samples to identify patterns of response to multiple treatments.

Neuroplasticity also underlies a range of changes in brain function and behavior involved in the development and persistence of addiction. For example, a landmark NIDA-funded study in mice identified a biological mechanism that could help explain how tobacco products could act as gateway drugs, increasing a person's future likelihood of abusing cocaine and perhaps other drugs as well. Mice that were exposed to nicotine for a week showed an increased response to cocaine. This effect depended on nicotine-induced changes in the structure of the tightly packaged DNA molecule that reprogram the expression pattern of specific genes, including a gene linked to the switch from acute to chronic drug effects. If nicotine is found to have similar effects in humans, these findings suggest that effective smoking prevention efforts would not only prevent the negative health consequences associated with smoking but could also decrease the risk of progression and addiction to cocaine and possibly other illicit drugs.

Several examples of maladaptive plasticity have been observed in pain disorders. Opioid analgesics are the most powerful medications currently available to treat chronic pain, but they can unfortunately result in addiction, tolerance, and physical dependence, limiting their value in some patients. 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.

NIH funds research on understanding and identifying the multiple and varied contributions of dysfunctional changes in the central nervous system that lead to and maintain persistent pain. For example, work supported by NIH is exploring the role of increased activity of neurotransmitters in enhancing neuronal activity in response to pain. NIH- funded research has also demonstrated the role of increased activity in certain brain structures in amplifying pain signals or causing or maintaining persistent pain. For instance, repeated activation of certain brainstem neurons (neurons in an area of the brain that regulates basic functions such as breathing and heart rate) causes an increase in their activity associated with a transition from episodic to chronic daily headaches.

NIH-supported researchers also have reported new findings on the mechanisms that lead to neuropathic pain induced by nerve injury. 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. In contrast, the new 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. Future treatments targeting glia may provide a way to halt the maladaptive signaling cascade that results in neuropathic pain. NIH also supports efforts to exploit adaptive plasticity at the level of brain networks for therapeutic pain intervention. Using real-time brain imaging, researchers have shown that patients with chronic pain can learn to exert voluntary control over activation of a particular brain region involved in pain perception and its regulation, effectively reducing the impact of their painful sensations. Future research will focus on the question of whether neuroimaging profiles 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.

NIH is playing a key role in the new Interagency Pain Research Coordinating Committee, which 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 will work to identify critical gaps in basic and clinical research on the symptoms, causes, and treatment of pain, and coordinate pain research activities across the federal government with the goals of stimulating pain research collaboration.

Although plasticity can lead to changes in neural activity patterns throughout life, the adult human brain and spinal cord have a limited capacity to replace or repair neurons 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. In one study, researchers showed that the vitamin folate (also known as vitamin B9) promotes healing in damaged rat spinal cord tissue by stimulating DNA modifications. The concern for U.S. Representative Gabrielle Giffords following a brain injury resulting from a gunshot, as well as the high rate of TBI among military personnel, has also increased attention on recovery, rehabilitation, and brain plasticity. Recently 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. Examples include investigations on dietary interventions to correct metabolic changes following TBI; the beneficial effects of exercise on plasticity; and brain imaging studies addressing how forced-use behavioral therapy affects the brain reorganization that underlies motor recovery. ARRA-funded research grants in this area include testing standards for data collection and outcome research from rehabilitation centers, and assessing a home stroke rehabilitation system that includes user-friendly home therapy robots and a tele-rehabilitation system. A National Center for Medical Rehabilitation Research-funded project is studying the effects of home-based care for pediatric TBI patients in Latin America, where the incidence of TBI is three times the

world average. The same project is also developing a data registry and improving the research infrastructure for future pediatric TBI research in Latin America.

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 between 2010 and 2030, 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 that may slow or even stop disease progression. Initially supported through ARRA funds, the iPS Cell Consortium is developing induced pluripotent stem (iPS) cells in three neurodegenerative diseases (Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS)) for use in disease mechanism studies and preclinical therapy. In FY 2011, NINDS announced continued support for the iPS cell consortia through a public-private partnership with industry, non-government organizations, and the California Institute for Regenerative Medicine.

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, though some inherited forms of the disease become symptomatic in middle age. AD slowly impairs memory, thinking skills and, eventually, the ability to carry out the simplest tasks of daily living. NIH-supported basic research on AD mechanisms has contributed in recent years to the development of new drug treatments. Although these treatments can help to manage symptoms in some people, they cannot cure this devastating disease.

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. Ongoing research initiatives include:

- The Dominantly Inherited Alzheimer's Network (DIAN) is a consortium of scientific investigators that recruit, study, and follow individuals from families with early onset dominantly inherited AD, a rare form of the disease. Understanding the sequence of brain changes in early-onset AD patients could provide insight into the more common late-onset form of the disease.

- 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. For example, NIA-funded investigators have recently developed a mouse model that expresses human tau, one of AD's pathological hallmarks, and discovered that tau pathology is transmitted from cell to cell, beginning in the brain's entorhinal cortex and spreading from one brain region to the next. This discovery provides insight into AD's earliest

development and offers a model for testing mechanisms and functional outcomes associated with disease progression.

- Through an initiative within the NIH 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 genome wide association studies 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.

- The AD Neuroimaging Initiative (ADNI, Phase II) 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 supports studies leading to the submission of an IND application to the FDA, a prerequisite for beginning human trials of potential new therapies.

- Human Cell Reprogramming for Aging and AD is a ground-breaking initiative supporting the development of iPS cells to facilitate the study of the genetic, molecular, and cellular mechanisms underlying human aging and 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 pilot trial on a nasal-spray form of insulin to delay memory loss and preserve cognition, a study of brain amyloid deposits in healthy people as a predictor of AD risk, and the ADNI cerebrospinal fluid biomarker study, which may aid the development of a diagnostic test for the early stages of 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 changes in the brain and body fluids are due to AD.

Parkinson's disease (PD) ranks among the most common late-life neurodegenerative diseases, with a prevalence of 1 percent in individuals over the age of 60. NIH-supported research has identified 10 new genetic mutations as risk factors for PD, revealed the benefits and risks of deep brain stimulation in PD patients, determined that tai chi improves balance and stability in patients with PD more than resistance training or stretching, and developed a novel strategy for deriving dopamine neurons from human pluripotent stem cells. Ongoing research efforts continue to uncover new gene mutations associated with increased risk for PD. NINDS is establishing the PD Biomarkers Program, which will support clinical and laboratory-based research projects, as well as bio-repository and data management resources to

accelerate biomarker discovery. NINDS also supports numerous investigator-initiated grants covering a variety of research priority areas, including the detection of genetic and environmental risk factors, identification of molecular and neurophysiological determinants of PD, and the development of technologies and therapeutics to improve symptoms or halt the progression of the disease. In addition, NINDS and NIEHS support numerous PD-related resources, research centers and clinical trials. For example:

- NINDS currently funds 10 Morris K. Udall Centers of Excellence across the country. These centers, which were authorized by the Morris K Udall Parkinson's Disease Research Act of 1997, provide a collaborative, interdisciplinary framework to accelerate PD research.

- The Centers for Neurodegeneration Science (CNS) Program strengthens the interchange among geneticists, clinicians, epidemiologists and scientists engaged in PD research. Three NIEHS-funded CNSs (UCLA, Emory University, and the Sanford Burnham Institute) are now exploring the interaction of environmental risk factors (e.g., agricultural pesticides) with proteins and pathways implicated in genetic forms of PD.

- The NIH Exploratory Trials in PD (NET-PD) program supports clinical trials conducted at more than 50 centers across the U.S. and Canada and designed to evaluate drugs that slow PD progression. NET-PD is conducting a Phase III clinical trial of creatine in patients with PD and is currently recruiting patients for a pilot study to test the safety and tolerability of pioglitazone, an FDA-approved drug that may prevent neuronal loss in PD.

- Other clinical trials funded by NINDS include a Phase III trial designed to compare the efficacy and tolerability of antidepressants in PD patients, and a multicenter Phase II study initiated in 2011 to determine whether moderate and/or vigorous exercise reduce PD symptoms in newly diagnosed patients.

Many of the leading causes of blindness are due to neurodegenerative diseases. In retinitis pigmentosa, genetic mutations in key proteins cause light-sensitive photoreceptor cells to die. NEI researchers are testing gene therapy to treat some of these diseases, and have published very promising gene replacement clinical trial results for a form of Leber's congenital amaurosis, a retinal degenerative disease caused by a mutant enzyme. Stargardt's 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 the photoreceptors, ultimately causes the neurons to die as well. In a clinical trial started in 2011, Advanced Cell Technology, Inc. transplanted RPE derived from human embryonic stem cells in patients with Stargardt's and AMD. Although many neurodegenerative diseases may be caused by rare mutations, NEI is funding research on more general therapy options using neurotrophins, factors that function to protect neurons from degeneration and may be able to rescue neurons at risk of loss through neurodegeneration, no matter the cause.

Moreover, neurons are not unique in their vulnerability to 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 six congressionally-mandated Paul

D. Wellstone Muscular Dystrophy Cooperative Research Centers[189] (also see the section on Wellstone MD Cooperative Research Centers in Chapter 4), as well as several initiatives for translational research. A public-private partnership funded by NIH, Parent Project MD, and PTC Therapeutics has made significant progress in identifying and optimizing small molecules that alter the levels of target proteins involved in the pathophysiology of MD. Other translational projects with public-private funding include a study focused on developing the peptide, biglycan, as a therapeutic for MD, and the first translational cooperative agreement for therapy development in myotonic dystrophy, the most common adult form of MD. The NIH Therapeutics for Rare and Neglected Diseases (TRND) Program has also accepted two MD projects for therapeutic co-development with biotech partners.

Other projects supported by NINDS and NIAMS focus on non-invasive imaging methods to track disease progression, and on understanding the molecular mechanisms underlying those forms of MD that are not yet at the stage of therapy development, such as congenital MD. NIAMS has recently funded a new Center of Research Translation of Systemic Exon-Skipping in MD, which will test the therapeutic potential of molecules that promote the production of a modified, but functional, form of the protein dystrophin. NHLBI also funds a number of basic and translational projects to investigate the basis for cardiac muscle disease in MD, and develop and evaluate novel therapies to prevent or restore dystrophin expression.

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 topics including studies on genetic and environmental risk factors; basic research on myelination, demyelination, and neuron degeneration; the blood-brain-barrier breakdown in MS; the immune system function in the central nervous system; optic neuritis (visual impairment due to inflammation or demylenation 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, NINDS supports a randomized, double-blind Phase III trial comparing the efficacy of treatment combining two FDA-approved MS medications (beta-interferon and glatiramer acetate) versus treatment with either agent alone for relapsing-remitting MS (CombiRx). Preliminary results showed that the combined treatment decreases the rate of brain lesions but was no more effective than either agent alone for reducing the risk of relapse. An ancillary study of CombiRx aims to identify gene and protein biomarkers of disease progression and treatment response in patients with relapsing-remitting MS. In addition, other Phase I/II clinical trials, including studies conducted at the NIH Clinical Center, are investigating the safety and efficacy of immunotherapies, mesenchymal stem cells, nutritional supplements, and hormonal treatments.

[189] For more information, see http://www.nichd.nih.gov/research/supported/mdcrc.cfm.

Advancing Neuroscience Research through Collaboration

Federal neuroscience research involves collaboration across NIH, HHS, and several other executive branch departments, including the Department of Defense (DoD), the Department of Veterans Affairs (VA), and the Department of Education (ED). For example, NIH ICs have a long history of collaboration with DoD and the VA on TBI research, including a long-term study of the neuropsychological outcomes associated with TBI among Vietnam War veterans and the development of the Federal Interagency TBI Research informatics repository.

Since its inception in 2004, the NIH Blueprint for Neuroscience Research 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 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, the Blueprint has announced new Grand Challenges initiatives focused on understanding the connectivity of the human brain, neuropathic pain, and the development of treatments for brain disorders.

- The Human Connectome Project is an ambitious effort to map the neural pathways that underlie human brain function. The project will lead to major advances in our understanding of what makes us uniquely human and will set the stage for future studies of abnormal brain circuits in many neurological and psychiatric disorders.

- The Blueprint Neurotherapeutics Network 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.

- The Grand Challenge on Pain supports research to understand the changes in the nervous system that cause the transition from acute to chronic pain, which can be an issue in TBI, stroke, spinal cord injury, and other conditions. One goal of the initiative is to enhance collaboration between researchers in the pain field and those with expertise in neuroplasticity

Other recent NIH Blueprint for Neuroscience Research initiatives include:

- The Non-Human Primate Atlas of detailed gene expression patterns in the developing rhesus macaque brain was created and hosted by the Allen Institute for Brain Sciences. This developmental neuroanatomical framework for exploring the cellular and molecular architecture of the developing postnatal primate brain has direct relevance for human brain development. The free online resource has a unique set of data and tools that allows viewing of indexed image sets searchable by gene, brain area and developmental stage, side by side with a high resolution Nissl/MRI atlas reference data set.

- The Blueprint K-12 Science Education funded eight science education grants that seek to improve and enhance neuroscience education in grades K-12 as well as inspire future generations of neuroscientists. The grants focus on providing innovative neuroscience education to children throughout the U.S. through a variety of mechanisms such as the development of interactive teaching modules that can be accessed on iOS devices (e.g., the iPad), innovative online games for classroom use, and museum exhibits that include interactive components as well as classroom activities.

- The Neuroscience Information Framework is a government-led project providing a dynamic inventory of online neuroscience resources—data, materials, and tools accessible via any computer connected to the Internet. The Framework advances neuroscience research by enabling discovery and access to public research data and tools worldwide through an open source, networked environment.

- The Gene Expression Nervous System Atlas is an NIH-funded, publicly available gene expression atlas of the developing and adult central nervous system in the mouse. It is also a source of mice genetically engineered to produce green fluorescent protein in different cell types within the nervous system.

Other NIH collaborative activities for neuroscience research include collecting and sharing clinical research data, which requires large investments in time and resources. However, currently there is no uniform way to help investigators implement NIH data-sharing policies for research on neurological disorders. In 2006, NINDS initiated an effort called Common Data Elements[190] to address this issue for many different disease areas. NINDS has worked with disease-specific experts and other stakeholders as part of this effort 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 data elements, and disease-specific elements for headache, spinal cord injury, stroke, epilepsy, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, Friedrich's ataxia, and multiple sclerosis, all of which are available on the website for use by investigators. A working group is currently developing data elements for several neuromuscular diseases, such as spinal muscle atrophy, Duchenne muscular dystrophy, traumatic brain injury, and myasthenia gravis.

Using FY 2009 ARRA funds, NIH is constructing the 293,839 square feet Porter Neuroscience Research Center Phase II, which will host cross-disciplinary researchers for seven ICs generating discoveries in structural biology, synaptic processing, sensory systems and sensory development, neuroenvironments, neurodevelopment and neurodegeneration, behavior, genetics, and high resolution microscopy.

The Joint NSF/NIH Initiative to Support Collaborative Research in Computational Neuroscience is a joint initiative among seven NSF Directorates and Offices, nine participating NIH ICs, and 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, emphasizing data sharing.

[190] For more information, see http://www.commondataelements.ninds.nih.gov/#page=Default.

NIH IC Directors participate in the Institute of Medicine 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, as well as effective clinical prevention and treatment strategies.

NIMH has partnered with the U.S. Army and DoD to carry out the Army Study to Assess Risk and Resilience in Service members (Army STARRS), the largest study of suicide and mental health among military personnel ever undertaken. The rate of suicide among Army soldiers has exceeded the civilian rate. 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.

NIH, in partnership with DOD, is building a central database for traumatic brain injury (TBI) research designed to promote data sharing and accelerate comparative effectiveness research on brain injury treatment and diagnosis. The Federal Interagency TBI Research database will serve as a central repository for new data, link to existing databases, and allow valid comparisons of results across studies. By collecting uniform and high-quality data on TBI, including brain imaging scans and neurological test results, the database will help to address current challenges associated with wide variation across studies in how data are collected and described.

The National Action Alliance for Suicide Prevention is a public-private partnership that includes representatives from NIH, CDC, the Substance Abuse and Mental Health Services Administration, the U.S. Army, and other federal entities. The Alliance's mission is to help guide the implementation of the goals and objectives set forth in the National Strategy for Suicide Prevention. NIMH is co-chairing an Alliance taskforce that aims to identify gaps in suicide research, including neuroscience research, that demonstrate promise in advancing the goal of reducing suicide through prevention.

NIMH provides leadership to the HHS Interagency Autism Coordinating Committee and works with other ICs, multiple HHS agencies, ED, and private research foundations to coordinate a national strategy for research on autism spectrum disorder. Each year, the Committee releases an updated Strategic Plan for Autism Spectrum Disorder Research.

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 2010–2011, the Consortium was proactive in coordinating a number of pain research initiatives and activities at NIH, which included identifying key opportunities in pain research and education, convening conferences and workshops to highlight recent advances and needs in the field, and building collaborations with other federal agencies, such as the FDA, and academic institutions involved in pain research.

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. NIH research in this area focuses on healthy developmental processes and the ways in which these processes diverge, causing or contributing to much of the nation's heavy burden of disease and disability. Some disorders of altered developmental processes, such as neural tube defects, are apparent at birth. Others, including intellectual and developmental disabilities, obesity, cardiovascular and metabolic diseases, cancers, mental illnesses, and dementias, may not emerge until months, years, or decades later.

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. This means that the developmental aspects of NIH research have critical implications for public health. 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 are now also being linked to the risk of non-communicable diseases such as diabetes, cardiovascular disease, 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 non-communicable diseases.[191]

This area of NIH research also encompasses medical rehabilitation, including 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 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, it 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

[191] Alwan A. *WHO Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases*. Geneva, Switzerland: World Health Organization, 2008. Available at: http://www.who.int/nmh/Actionplan-PC-NCD-2008.pdf.

insights into the trajectories of human development and disease and even to harness developmental processes such as cell differentiation 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.

As the institute with statutory responsibility for child health and human development research, NICHD conducts and supports research programs in reproductive health and in the developmental processes that begin before conception and continue through adolescence. As the Institute with statutory responsibility for research on aging, 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 managing and eliminating symptoms caused by illness, and it also is the designated lead institute for end-of-life research. NIEHS focuses on the influences of environmental agents on the development and progression of specific diseases.

Numerous other ICs support life stages, human development, and rehabilitation research in cancer, diabetes, addiction, mental health, musculoskeletal and neurological disorders, and other areas relevant to their missions. ORWH, among 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 and sex and gender differences in disease. Mission-specific rehabilitation research is supported by multiple Institutes, including NEI, NIA, NIBIB, NICHD, NIDCD, NIDCR, and NINDS. A focal point for this research is NICHD's National Center on Medical Rehabilitation Research, which emphasizes the rehabilitation and lifelong care of people with physical disabilities resulting from stroke, injury, and other disorders.

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, cardiovascular disease, pregnancy complications, certain cancers, osteoarthritis, liver and gall bladder disease, and depression. CDC estimates the prevalence of obesity among individuals ages 20 years and older in the U.S. as 35.7 percent, and the prevalence of obesity plus overweight as 68.8 percent.[192] Overweight and obesity also exert a substantial economic toll on the U.S., with the combination of direct health care costs plus indirect costs, such as lost wages caused by illness, estimated to be $117 billion for the year 2002.

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 Institute of Medicine (IOM) defines disability as impairments in body structure or function, limitations

[192] Flegal KM, et al. *JAMA.* 2012;307(5):491–7. PMID: 22253363.

on activities such as dressing and other daily personal care, and limitations on participation in such activities as school and work. IOM reported that between 40 million and 50 million individuals,[193] 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 $458 million in FY 2010 and $459 in FY 2011 for non-ARRA (regular appropriations) and $93 million in FY 2010 for ARRA appropriations.[194] 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, or even preempting the disease process before it starts. 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. 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, and 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.

Human Development

In studies of the most fundamental molecular and cellular processes, NIH scientists continually expand understanding of how development typically progresses, what goes awry and why, and how health is affected. For example, epigenetic influences on the expression of genes may be critical mechanisms for gene/environment interactions that influence health and development. Understanding these subtle interactions is an essential step toward discovering treatments and preventive strategies. NIH has established the Common Fund Epigenomics Program 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). Among other things, Common Fund epigenomics resources may become

[193] For more information, see http://www.nap.edu/openbook.php?record_id=11898&page=1.
[194] For funding of various Research, Condition, and Disease Categories (RCDC), see http://report.nih.gov/categorical_spending.aspx.

the basis for studies of diabetes, including the effects of the intrauterine environment on later risk of disease development.

Basic research in developmental biology also may enable scientists to harness powerful normal cellular processes for therapeutic purposes. Research on cell senescence, a significant factor in normal aging, one day may yield understanding of cellular mechanisms that act to block the development of cancer as well as specific characteristics of aging. Goals of human embryonic stem cell research include explaining critical events in early human development that could lead to developing customized regenerative medical interventions. Sex and gender differences affect developmental trajectories and disease risks. Basic research is only one essential component of the NIH portfolio of multiple methodological approaches to understanding human development. For example, with NIH support, investigators are assembling a unique database of anatomical neuroimages of children's brains over time. This database also will include clinical, behavioral, demographic, and cognitive data on the children, thus enabling scientists to understand the multiple dimensions of normal human brain development. This knowledge is also critical to understanding the effect of environmental "insults" to the brain, such as drug use during pregnancy. Such understanding is essential in elucidating intellectual and developmental disabilities, pediatric neurological diseases, and many other disorders that emerge in childhood. The multi-decade Baltimore Longitudinal Study of Aging (BLSA) has created a wealth of information that has helped scientists—and the public—understand distinctions between physical changes attributable to the aging process and those caused by disease. These data have yielded important insights on, among other things, relationships between age-related changes in the arteries and cardiovascular disease and differences between normal declines in cognitive ability related to age and those associated with Alzheimer's disease (AD) and related conditions.

Life Stages

"Life stages" or "life course" research is a concept that 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. The NIH-supported Breast Cancer and the Environment Research Centers (BCERC) 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. Specific attention is given to puberty, menopause, pregnancy, and other windows of susceptibility when the developing breast may be at particular risk from environmental exposures.

NIH-supported research on maternal and childhood obesity seeks to understand complex interactions among genetic, psychological, physiological, familial, community, environmental, and other factors in this major public health problem. The goals of such research include understanding the rapid, recent increases in rates of obesity and determining how and when to intervene to achieve lasting effect. NIH findings of high rates of overweight and other major risk factors for type 2 diabetes in middle school

students are the basis for current trials of school-based diet and exercise interventions. The goal of the interventions is to decrease the children's short- and longer-term risks for obesity and type 2 diabetes.

Research that led to universal newborn screening for phenylketonuria and for hypothyroidism and immediate initiation of treatment for affected infants to protect their developing brains has virtually eliminated intellectual and developmental disabilities (IDDs) associated with these conditions. NIH is funding a major initiative to speed the development of highly efficient technology for screening newborns for very large numbers of additional rare genetic conditions and to accelerate the discovery of treatments for such conditions. This initiative also includes support for networked facilities that can translate scientific discoveries quickly into clinical practice.

NIH investments in understanding and developing interventions for Fragile X and Down syndromes and other IDDs include support for 14 IDD centers. These centers provide core research resources in genetics and proteomics as well as clinical infrastructure for a wide range of studies. Multiple NIH-supported programs focus on autism spectrum disorder. For example, the Autism Centers for Excellence include (a) six centers focusing research on possible causes of autism spectrum disorder, including genetic, immunological, and environmental factors, and (b) five networks focusing on causes, preventive interventions, and improved treatment. High priority will be placed on identifying autism spectrum disorder risk factors, biological signatures of autism spectrum disorder, and evaluating interventions in understudied populations. NIH established an intramural research program to accelerate development and testing of innovative treatments for autism spectrum disorder. This program has already evaluated hundreds of children and tested three novel compounds.

Retinopathy of prematurity (ROP) is abnormal blood vessel development in the eyes of some infants born severely premature, which can lead to blindness if not treated in time. NEI is funding a clinical trial that uses telemedicine as a tool for doctors to remotely diagnose ROP in premature infants born in rural and underserved areas. Other pediatric vision research is addressing the increasing incidence of myopia (nearsightedness). Recent NEI research has found that the amount of time children spend outdoors may reduce the risk of developing myopia, whereas near work, such as reading a book or a computer screen, is not necessarily related to myopia and other refractive errors, as long hypothesized.

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. Recent studies have uncovered specific genetic variants linked to heightened risk of future drug problems in those who started using during adolescence. Researchers also are testing preventive strategies such as universal approaches that engage broad youth audiences to address a panoply of risk behaviors; selective interventions that target groups of individuals at increased risk (relative to the general population); indicated prevention interventions that focus on individuals who have begun using drugs but are not yet diagnosed with a disorder; or tiered interventions that include a combination of universal, selective, and indicated approaches. Better understanding of relationships between

developmental stages and disease processes may be critical to the efficacy of therapeutic interventions. In another example, NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development but with a significant delay in maturation of the prefrontal cortex between the ages of five and 15 years. Scientists now are investigating the effects of treatment on rates of cortical maturation.

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 over half a century. The main focus has been to describe physiological parameters and longitudinal trajectories of change in these parameters in participants of different ages, initially free of major diseases at the time of enrollment. The underlying goal is to discriminate 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 assessment of physiologic and biomarkers of aging and theoretical refinements, the BLSA continues to pursue the following objectives: (1) describe longitudinal trajectories of the major aging phenotypes, (2) identify genetic, physiological, behavioral and environmental factors that affect the rate of change in these phenotypes and (3) understand the interrelationship between aging phenotypes and highly prevalent chronic conditions and their independent and joint impact on age-related decline in physical and cognitive function.

In order to develop a comprehensive picture of the health and disability of older Americans, NIH supports the Health and Retirement Study (HRS) and the National Health and Aging Trends Study (NHATS). The HRS has surveyed more than 22,000 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, and health expenditures. Self-report and biomarker measures of health are combined with Medicare data on utilization of health services. ARRA funds have facilitated the expansion of the study to include participant genotyping and doubling the minority sample. The National Health and Aging Trends Study (NHATS) replaced the National Long-Term Care Survey as the source of research data on national disability trends and dynamics among the senior population of the U.S. This study has just completed the collection of baseline data, which will become available to the research community in spring 2012.

Clinical trials are being supported by NIH in order to understand the potential genetic factors that contribute to exceptional survival (the Long Life Family Study). These trials will test treatments for health conditions common to old age, including testosterone supplementation to delay or prevent frailty in older men; effects of exercise on mood, health, and cognition; and, an array of interventions for menopausal symptoms.

Research on normal maturational processes may lead to new ways to treat or prevent disorders associated with aging. NIH conducts and supports a large and diverse portfolio of research on aging and age-related diseases and conditions, including the biochemical, genetic, and physiological mechanisms of aging in humans and animal models; structural and functional changes in the aging nervous system; social and behavioral aspects of aging processes and the place of older people in society; and the pathophysiology, diagnosis, treatment, and prevention of age-related diseases, degenerative conditions, and disabilities. 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.

NIA's Interventions Testing Program (ITP), which began in 2003, supports the testing of 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 lifespan in both male and female mice. Further research is ongoing.

Age-related macular degeneration (AMD), the leading cause of blindness in older Americans, will impose an increasing burden in future years as the baby boomer generation ages. The Age-Related Eye Disease Study (AREDS) demonstrated that antioxidant vitamin and mineral supplements reduced the progression to advanced AMD by about 25 percent. Building on these landmark findings, the follow up study is assessing additional supplements (lutein, zeaxanthin, and long-chain omega-3 fatty acids) as a treatment for AMD and cataracts. It is also evaluating effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression.

NIH makes major investments in research to understand the onset and progress of Alzheimer's disease, the most common form of dementia in aging, and to discover how to slow its progress and, ultimately, to prevent it. In April 2010, NIH held a *State of the Science Conference on Preventing AD and Cognitive Decline* in which the conference panel determined that there is insufficient scientific evidence to support use of any interventions to prevent cognitive decline or Alzheimer's disease. In 2009, expert panels convened by the NIA and Alzheimer's Association began meeting to update the clinical diagnostic criteria for the disease. Completed in April 2011, the NIA/Alzheimer's Association Diagnostic Guidelines for Alzheimer's disease established a paradigm for diagnosing and researching the disorder. The updated guidelines cover the full spectrum of Alzheimer's disease as it gradually develops over many years and addresses the use, primarily in the research setting, of brain imaging and biomarkers that may help diagnose Alzheimer's disease at earlier stages.

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 end-of-life research applies biological, behavioral, and social science strategies to advance the understanding of the dynamic interactions of these various factors and

to develop interventions that optimize patient and caregiver quality of life across care settings and cultural contexts. NIH recently sponsored an initiative to develop and test interventions to enhance end-of-life and palliative care, which providers can implement across multiple settings, illnesses, and cultural contexts. NIH-supported Centers in Self Management or End-of-Life research are important loci for interdisciplinary research in this area. In August 2011, NINR, in partnership with NIA, NCCAM, ORDR, ORWH, and the NIH CC Office of Bioethics, convened a three-day national summit on "The Science of Compassion: Future Directions in End-of-Life and Palliative Care." The summit examined the state of research and clinical practice in end-of-life and palliative care and provided an opportunity for scientists, health care professionals, and public advocates to come together to catalyze and shape the future research agenda for this critical scientific area.

Rehabilitation

The goal of rehabilitation science is to enable individuals with functional impairments associated with congenital disorders, chronic diseases, or events such 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, psychosocial trajectories, and expected lifespan, must all be taken into account in rehabilitation interventions.

An important focus of rehabilitation research is the interface between medicine and engineering. Scientists explore innovative biomedical technologies and test their capacity to resolve stubborn medical problems and enhance mobility, sensory, and other functions of individuals with disabling conditions. NIH projects in rehabilitation neuroscience also pursue the development of prosthetics 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. Researchers are capitalizing on new advances in technology that resulted in a successful prototype "bionic arm" to create a next-generation "bionic hand." Rerouting nerve endings and attaching more electrodes could restore a rudimentary sense of touch and allow users to control robotic fingers with their brain.

Basic processes of cellular and molecular development and function offer great potential for rehabilitation research and clinical applications. Scientists are seeking to understand both the mechanisms that underlie functional impairments and the therapeutic potential of such basic developmental processes as cell differentiation. A major collaboration between the NIH intramural program and the Department of Defense is the new Center for Neuroscience and Regenerative Medicine (CNRM) whose mission is to enhance the health, productivity, independence, and quality-of-life of people with disabilities by supporting a broad range of research, including efforts to understand the underlying biology of injury and disability, and the body's normal mechanisms of recovery and adaptation. These activities include a special emphasis on research related to spinal cord injury (SCI), traumatic brain injury (TBI), and stroke. The Center's mission also includes catalyzing advances in treatment, rehabilitation, and long-term recovery for individuals experiencing TBI. Even seemingly mild forms of TBI can seriously disrupt short- and long-term brain function. Because past studies of single agents were largely unsuccessful in improving TBI outcomes, new efforts involve multiple drug combinations and molecules to inhibit swelling, inflammation, and other biochemical reactions that can

harm brain tissue after TBI. One such combination under study is progesterone and vitamin D. Progesterone is known to protect the brain from injury; however, it is much less effective in individuals who have low levels of vitamin D. Other efforts address the difficulties with concentration and attention often reported by individuals with TBI. One relevant project compares the effectiveness of behavioral therapy, centered on improving concentration and emotional control, to drug treatment with methylphenidate, often prescribed for attention deficit disorder.

The Clinical Center is working with many ICs in leading the investigator-coordinated NIH intramural Bone Marrow Stromal Cells (BMSC) Transplantation Center, where clinical grade BMSCs, shown to have a therapeutic effect on several injuries and diseases, are being produced and used for the treatment of patients with acute graft-versus-host disease. Ultimately, the BMSCs produced by this Center could be used for the treatment of a variety of human diseases and disorders.

NIDCR supports interdisciplinary basic and translational research for engineering and regeneration of functional oral and craniofacial tissues, including research aimed at improving the capacity of oral and craniofacial tissues to heal and regenerate themselves with the help of a variety of novel therapeutic agents. In one example, NIDCR is supporting a study that demonstrates how mechanical forces originating outside a cell become transmitted into cell's nucleus to direct early tooth development. This advance will help to derive new approaches that employ mechanical and other biophysical forces to mimic early developmental events for regeneration of an adult tooth, and has important implications for skeletal bone development as well.[195]

NIH participates with DoD and other agencies for the Armed Forces Institute of Regenerative Medicine in a multi-agency effort to develop and advance treatment options for severely wounded service men and women (http://www.nibib.nih.gov/About/Overview/DDSTFactSheet and http://www.afirm.mil/). Research projects aim to develop new products and therapies to address the growing prevalence of complex and life-threatening injuries and help those who have been wounded to reach their highest potential. Research projects are advancing wound healing therapies that prevent and manage scar formation; developing novel treatments to reduce the high morbidity and mortality from burn wounds; developing therapies that promote regeneration of bone material for craniofacial reconstruction; and developing finger and limb reconstruction, regeneration or transplantation.

[195] Mammoto T, et al. *Developmental Cell*. 2011;21 (4): 758–769). PMID: 21924961.

Chronic Diseases and Organ Systems

Chronic diseases are defined by HHS as conditions that last a 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, seven of every 10 Americans who die each year—more than 1.7 million people—succumb to a chronic disease.[196] Health-damaging behaviors such as drug use (e.g., tobacco, excessive alcohol, or other drug), lack of physical activity, poor eating habits, and obesity, contribute to many chronic diseases, whereas others may result from the long-term effect of early exposure to toxins or other environmental factors, especially in individuals with a higher genetic risk of disease. Some 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 (with its attendant poor nutrition and health care), and they may suffer the adverse health consequences earlier. For these reasons, modern medicine requires an integrated understanding of the complex interactions among multiple organs, the nervous system, the circulatory system, the immune system, and the endocrine system.

A shared aspect of many chronic diseases is chronic pain and other disease-associated disabilities that interfere with quality of life. A recent study shows that approximately 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined—suffer from chronic pain.[197] As many as 75 million Americans suffer from two or more concurrent chronic conditions,[198] placing them at risk for worse overall health and significant financial burden, including higher prescription drug and total out-of-pocket health care spending.

Thus, research to combat chronic illness involves significant trans-NIH collaboration in addition to the mission-specific work of each IC. NIH supports basic research on both normal and disease states of organ systems to understand the initiation and progression of chronic diseases, as well as 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),

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[196] Centers for Disease Control and Prevention, Chronic Diseases: The Power to Prevent, the Call to Control. Atlanta, GA, 2009. Available at http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm.

[197] Committee on Advancing Pain Research and Education, 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.

[198] Hwang W, et al. *Health Affairs.* 2001;(20)268–9. PMID: 11816667.

"Neurosciences" (e.g., Parkinson's disease, Alzheimer's disease, autism, and epilepsy), "Autoimmune Diseases" (e.g., lupus, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel diseases), and "Infectious Diseases and Biodefense" (e.g., HIV/AIDS and viral hepatitis). Because some people with certain chronic diseases require transplantation to replace a diseased organ or tissue, 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) are highlighted in this section. Research on complementary and alternative medicine (CAM) 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 were highlighted in the Neuroscienc section.

The prevalence and burden of chronic diseases are substantial. About 133 million Americans—nearly half of adults—live with at least one chronic illness.[199] Chronic disease disables or limits activity for almost 12 percent of all adults, including more than one-third of adults ages 65 and older.[200] 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 multiple chronic diseases 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.[201]

Many chronic diseases that lead to significant disability develop over time and become more prevalent with age (e.g., osteoarthritis, chronic kidney disease, vision loss). Less commonly, chronic disease 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, asthma). Some chronic diseases are common in the U.S. population, as in the case of heart disease, which is the leading cause of death, while others are relatively rare, such as cystic fibrosis, 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.

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 2015, chronic diseases will be the most common cause of death even in the poorest countries. In 2005, chronic diseases contributed approximately 60 percent of the 58 million total deaths in the world and almost three-quarters of the burden of disease (measured in disability-adjusted life-years[202]) in those ages 30 or older.[203]

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[199] Centers for Disease Control and Prevention, Chronic Diseases: The Power to Prevent, the Call to Control. Atlanta, GA, 2009. Available at: http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm.
[200] National Center for Health Statistics. Health, United States, 2008 with Chartbook. Hyattsville, MD, 2009.
[201] Centers for Disease Control and Prevention, Chronic Diseases: The Power to Prevent, the Call to Control. Atlanta, GA, 2009. Available at: http://www.cdc.gov/nccdphp/publications/AAG/chronic.htm.
[202] Disability-Adjusted Life Years (DALYs) are years lost due to a disability. DALYs are used to measure the overall burden of a disease.
[203] Quam L, et al. *Lancet.* 2006;368(9543):1221–3. PMID: 17027712.

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 H 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 that table cannot be used to provide an aggregate number.

Summary of NIH Activities

NIH invests significant resources in 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. 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/Heart Diseases

Cardiovascular disease (CVD) is a broad term used to encompass many conditions, including heart diseases such as coronary heart disease, cardiomyopathy, heart failure, heart valve disease, sudden cardiac arrest, and congenital heart defects and various diseases and conditions of the blood vessels such as cerebrovascular disease (stroke), 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.

As the lead institute for CVD research, NHLBI studies cover the spectrum of basic investigations, clinical and translational research, and implementation and dissemination research. About two-thirds of the nearly 4,000 CVD-related grants and research contracts funded by NHLBI involve basic research. The clinical research funded by NHLBI includes observational studies, randomized clinical trials, comparative effectiveness research, implementation and dissemination research, and clinical studies of the effect behavioral and psychosocial factors on CVD and risk.

The Institute's strong focus on basic and early translational studies is exemplified by support for large programs, many of which provide essential resources for investigators to conduct cutting-edge studies in areas such as genomics and cell therapy. For example, the Candidate Gene Association Resource *(CARe)* is a shared resource for analyses of the association of genotypes with phenotypes relevant to the NHLBI mission. It comprises nine NHLBI-sponsored cohort studies—Atherosclerosis Risk in Communities

(ARIC), Cardiovascular Health Study (CHS), Cleveland Family Study (CFS), Coronary Artery Risk Development in Young Adults (CARDIA), Framingham Heart Study (FHS), Jackson Heart Study (JHS), Multi-Ethnic Study of Atherosclerosis (MESA), and Sleep Heart Health Study (SHHS).

The NHLBI Pediatric Cardiac Genomics Consortium is a cooperative investigative group that conducts clinical and translational research on the genetic causes of congenital heart disease and genetic contributions to outcome in individuals with congenital heart disease. In addition, 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. Finally, 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.

NHLBI supports a robust portfolio of clinical research, including clinical trials 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 to reduce the rate of recurrent myocardial infarction (heart attack), stroke, and CVD-related death. Clinical trials are also underway to improve treatment for arrhythmia. 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 one to determine whether a target of lower blood pressure than current standards will reduce the risk of heart and kidney disease, stroke, and/or age-related decline in cognitive function. To better treatment of heart failure, NHLBI supports clinical trials to test the benefit of mechanical circulatory support therapy using ventricular assist devices, surgical intervention, and medical therapy.

NHLBI supports numerous trials to improve the treatment of pediatric heart disease. For example, The Pumps for Kids, Infants, and Neonates (PumpKIN) program is testing devices to help children born with congenital heart defects or children who develop heart failure. The Therapeutic Hypothermia after Pediatric Cardiac Arrest trial is evaluating whether regulating body temperature will improve the outcome for children after cardiac arrest.

NHLBI also supports a number of collaborative research infrastructure projects to enable the conduct of clinical trials in areas of identified need and opportunity. For example, the Cardiovascular Cell Therapy Research Network provides an infrastructure to evaluate innovative cell therapy strategies for individuals with CVD, and the Cardiothoracic Surgical Trials Network enables rigorous scientific comparisons and evaluation of newer surgical techniques, devices, and innovative pharmaceutical and bioengineered products to improve CVD outcomes in adult populations.

NHLBI supports an extensive portfolio of behavioral research, including many studies to develop and evaluate interventions for improving eating and exercise patterns to promote cardiovascular fitness, prevent weight gain, or promote weight loss. In addition, NHLBI Global Health Centers of Excellence

support a worldwide network of research and training centers to prevent and control chronic diseases, including CVD. Each center is led by a research institution in a low- to middle-income developing country that is paired with at least one partner academic institution in a developed country to enhance research and training opportunities.

Other NIH institutes also support CVD research. For example, stroke research at NINDS is comprehensive and includes research to obtain a better understanding of basic disease mechanisms; epidemiology studies to assess stroke risk, occurrence and outcomes in the population; clinical research to develop effective prevention and acute treatment approaches; and development of strategies for improving recovery and rehabilitation in stroke patients. A number of NIH stroke trials are conducted through the NINDS Specialized Program of Translational Research in Stroke, a network of eight research centers across the country that is focused on improving management and outcomes of acute stroke.[204]

NIBIB supports a group of interdisciplinary researchers working to develop a new method of mechanical circulatory support and a total 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 device manufacturers to improve the design of these mechanical devices.[205] [206] 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 healthcare costs.

Investments in CVD basic research have produced any number of scientific advances. For example, many genetic factors have been identified that influence blood pressure. In one study, an international team of scientists examined the genomes of 200,000 people, looking for DNA variants related to blood pressure. The study found a number of previously unsuspected variants that influence blood pressure, providing new insights into the genetics and biology of blood pressure.[207] NHLBI-supported scientists have reported development of a three-dimensional model of the main protein component of HDL as it occurs naturally in the body. HDL's nickname "good" cholesterol comes from its ability to grab artery-clogging cholesterol from cells and help dispose of it. Knowing the structure of this HDL protein should help researchers mimic its function and perhaps ultimately develop new drugs to mimic its function and prevent atherosclerosis.[208]

In 2011, researchers reported analysis of health outcomes in postmenopausal women participating in the Women's Health Initiative estrogen-alone trial who had undergone a hysterectomy and had taken estrogen for an average of six years. They found that excess rates of stroke and blood clots among estrogen users – reasons for halting the trial in 2004 – disappeared during the subsequent four years.

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[204] For more information, see www.spotrias.org.
[205] Girdhar G, et al. *PLoS One*. 2012;7(3):e32463. PMID: 22396768.
[206] Rowley JW, et al. *Circ Cardiovasc Interv*. 2012;5(2):296–304. PMID: 22511738.
[207] The International Consortium for Blood Pressure Genome-Wide Association Studies. *Nature*. 2011; 478(7367):103–9. PMID: 21909115.
[208] Huang, R. et al. *Nat Struct Mol Biol*. 2011;18(4):416–22. PMID: 21399642.

Estrogen use during the trial did not increase or decrease the risks of death, heart disease, colorectal cancer, or hip fractures but did decrease breast cancer risk.

New findings are promising revolutionary new approaches to CVD treatment. For example, a recent study promises a potential new mechanism for repairing the heart after a heart attack. The heart's natural capacity to repair itself is limited, and even when able to recover, resulting scar tissue impairs its ability to pump blood. Recent research showed that non-muscle, "fibroblast" cells, which make up more than half the cells in the heart, can be reprogrammed into other cell types — including muscle. Scientists identified a trio of gene-controlling proteins that, when "turned on", converted these fibroblasts in an injured mouse heart into beating heart muscle cells.[209]

Results from a large clinical trial that compared surgical removal of artery-narrowing plaque to insertion of a metal tube or stent to reopen narrowed neck arteries showed that both are safe and effective in preventing stroke. However, younger patients (aged < 70 years) fared better with stenting and older ones (aged > 70 years) with surgery. Based in large part on these results, an FDA panel voted to widen the use of carotid stenting, which will impact patient care.[210]

NIDDK supports research on CVD as a common and devastating co-morbidity 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 NIDDK-led Look AHEAD (Action for Health in Diabetes) clinical trial is determining whether a lifestyle intervention designed to promote weight loss can improve health outcomes, including prevention of heart disease, in obese people with type 2 diabetes. The NIDDK is also 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. Similarly, new information about the relationship between CVD and type 2 diabetes should come from the Diabetes Prevention Program Outcomes Study, a long-term follow up to the landmark Diabetes Prevention Program clinical trial. Another large scale effort, the Chronic Renal Insufficiency Cohort study, co-sponsored by NIDDK and NHLBI, is evaluating long-term cardiovascular risk and outcomes in persons with chronic kidney disease.

Stroke research continues to make considerable advances, but there remain challenges that current and future research efforts will need to overcome, including neuroprotection strategies, disparities in stroke risk and burden, and expanding the time window for safe and effective use of tissue plasminogen activator (tPA) in breaking down blood clots. The NINDS Stroke Progress Review Group is undertaking a five year review of challenges and priorities in stroke research and a new NINDS planning effort is currently underway to identify the most promising opportunities in stroke prevention, treatment and recovery research. NHLBI is currently updating the adult clinical practice guidelines for hypertension,

[209] Ieda M, et al. *Cell*. 2010 Aug 6;142(3):375–86.PMID: 20691899.
[210] Mantese VA, et al. *Stroke*. 2010;41(10 Suppl):S31–4. PMID: 20876500.

cholesterol, and obesity, all of which are risk factors for developing CVD. The project uses state-of-the-art methodology for systematic evidence reviews and guideline development. Following completion of these guidelines NHLBI will undertake the development of integrated CVD risk reduction guidelines.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a serious but largely preventable lung disease that makes breathing difficult. It has two forms, emphysema and chronic obstructive bronchitis, that tend to coexist in most people. Emphysema and chronic obstructive bronchitis damage the lungs in different ways, but both make breathing difficult. COPD is the third most common cause of death in the U.S. More than 12 million Americans are currently diagnosed with COPD, and researchers estimate that 12 million more 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. Symptoms of COPD 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 the NIEHS are directed at uncovering the relationships between exposure to agents such as ozone, particulate matter, endotoxins, excessive heat, and other environmental triggers and cardiopulmonary disease. One such discovery may lead to more effective treatment of COPD; a researcher studying toxic red tides has isolated a substance from the algae called brevenal that acts as an antitoxin and has been shown in animal studies to prevent, reduce, and reverse bronchoconstriction at very low doses.[211]

Large, multi-center clinical trials are evaluating the efficacy of several treatments/therapies that are available for immediate use. The 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 deficiency). A trial conducted by NHLBI's COPD Clinical Research Network is testing whether simvastatin, a drug approved for cardiovascular diseases, can be used to reduce the frequency of COPD exacerbations. Another trial is comparing the long-term immune response of COPD patients to two different pneumococcal vaccinations.

Because COPD involves a wide range of abnormalities, different patients with COPD may require specific treatments. Studies are underway to define subgroups of patients for whom different therapeutic approaches should be used. The COPD Gene study is evaluating 10,000 current and former smokers, with and without COPD, to better categorize the various abnormalities seen on x-ray CT lung images and to identify genetic traits that are associated with specific manifestations of the disease. The 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. The SubPopulations and InteRmediate Outcome Measures in COPD Study will define subpopulations of COPD patients by extensive molecular and clinical phenotyping and will also identify intermediate outcome measures that can be used to improve the efficiency of future clinical trials.

[211] Nguyen-Huu TD, et al. *Toxicon*. 2010;56(5):792–6. PMID: 19682481.

COPD patients often suffer from multiple afflictions. For example, lung cancer is 4–5 times more frequent 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 recently awarded seven grants to promote research on the connections between these diseases of the lung, which together cause over a quarter of a million deaths in the U.S. each year.

A number of recent studies are pointing towards better medical approaches for treating COPD. An antibiotic was found to decrease the frequency of exacerbations and improve quality of life. A broccoli sprout derivative was found to potentially augment the anti-inflammatory effects of steroids in COPD. Researchers are testing new approaches to protect against cigarette-smoke induced damage to the lung. For example, using an animal model of emphysema, a recent study showed a prominent role for the enzyme superoxide dismutase in protecting mice from cigarette smoke-induced damage, suggesting that therapeutic interventions that augment SOD3 may be helpful.[212] In another animal model, investigators identified a protein that mediates the rate of cell degradation in mice exposed to cigarette smoke leading to epithelial cell death and alveolar space enlargement. This observation suggests another therapeutic target in emphysema.[213]

COPD is believed to have a strong genetic component. A genome-wide association study for COPD identified a potential gene related to susceptibility.[214] In another genome-wide association study, investigators identified several potential genes that may confer susceptibility in an area of the genome that has previously been associated with cigarette smoking behavior. In similar studies, regions of the genome were identified that could provide insight into the molecular mechanisms regulating pulmonary function.[215]

While the effect size of these genetic variants is small in comparison with the estimated effect of cigarette smoke exposure, the discovery of additional genetic risk variants for COPD is an important step toward the development of new preventative and therapeutic approaches for this disease. This work underscores the importance of gene environment interactions in determining individual susceptibility to COPD and findings in this area may have practical implications for disease prevention.[216]

As COPD accounts for more than 300 million patients worldwide, NHLBI is participating in discussions with the World Health Organization (WHO) and other international groups regarding 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, globally indoor air pollution also contributes to the risk for COPD. An NIH-wide workshop on indoor air pollution and cook stoves was held in 2011 that identified research strategies that could have important implications for preventing COPD globally.

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[212] Yao H, et al. *Proc Natl Acad Sci U S A*. 2010;107(35):15571–6. PMID: 20713693.
[213] Chen ZH, et al. *Proc Natl Acad Sci U S A.* 2010;107(44):18880–5. PMID: 20956295.
[214] Cho MH, et al. *Nat Genet*. 2010;42(3):200–2. PMID: 20173748.
[215] Soler Artigas M, et al. *Nat Genet*. 2011;43(11):1082–90. PMID: 21946350.
[216] Sørheim IC, et al. *Chest*. 2010;138(5):1125–32. PMID: 20595457.

Chronic Pain and Palliative Care

Many chronic diseases are associated with pain that can be chronic and severe. Pain often is difficult to treat and can significantly erode patients' quality of life. As discussed in the Neuroscience section, NIH supports a spectrum of pain research that includes basic science to understand the mechanisms of pain and pain relief, as well as clinical research to evaluate pharmacological, surgical, and alternative strategies for pain management. 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 and their families. Researchers also are 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 that can be applied in a variety of settings, illnesses, and cultural contexts.

Chronic pain is a debilitating symptom of many long-term disease states such as cancer or arthritis. It may also 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 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 damage to the peripheral nerves or to the central nervous system).

Many chronic pain conditions are co-morbid or overlapping in nature with two or more conditions occurring simultaneously in the same patient. It is likely that some of these overlapping disorders share common mechanisms including genetic susceptibility. Overlapping pain conditions may include migraine, chronic fatigue syndrome, endometriosis, fibromyalgia, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, temporomandibular joint disorders (TMJD), and vulvodynia. Chronic pain conditions can be exacerbated by environmental or psychosocial factors.

NIH funds a broad portfolio of chronic pain research activities ranging from basic research into the molecular, genetic, and bio-behavioral basis of chronic pain to large-scale clinical studies of potential treatments. NIH has leveraged various award mechanisms such as the Common Fund-sponsored Transformative Research Award Program, ARRA-funded NIH Challenge grants and Grand Opportunity grants as well collaborative funding through the NIH Blueprint for Neuroscience Research to fund cutting-edge pain research.

Pain research activities at NIH are coordinated in large part by the NIH Pain Consortium—a joint undertaking across 25 Institutes and offices that identifies and facilitates implementation of key opportunities in collaborative pain research. In 2010–2011, the Consortium was proactive in coordinating a number of pain research initiatives and activities at NIH which included identifying key

opportunities in pain research and education, convening conferences and workshops to highlight recent advances and needs in the field, and building collaborations with other federal agencies, such as the FDA, and academic institutions involved in pain research. For example, members of the Pain Consortium currently participate in an advisory committee for the Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) initiative, a public-private partnership program sponsored by FDA to streamline the discovery and development of analgesics. In 2011, Pain Consortium members established working groups for overlapping chronic pain conditions as well as chronic lower back pain. Led by NIDA and in collaboration with members of the Consortium 12 health professional schools in May 2012 were designated and funded as "Centers of Excellence for Pain Education" to develop, evaluate, and distribute pain management curriculum resources for medical, dental, nursing and pharmacy schools to advance the assessment, diagnosis, and safe treatment of pain while minimizing risks of addiction and diversion.[217]

In addition to Trans-NIH efforts, NIH ICs fund chronic pain research aligned with their missions through joint funding opportunity announcements (FOA), workshops, and conferences. For example, NINDS focuses on headache and neuropathic pain research. The Institute recently released a headache planning meeting report[218] detailing the opportunities, priorities, and recommendations for headache research. NINDS is funding a ten-year study on overlapping pain conditions that disproportionately affect women, including episodic migraines and is also funding 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.

In 2011, NEI created a new program for ocular pain and funded new projects to examine the neurons and pathways involved in corneal pain. NINR sponsors numerous training opportunities to develop improved research capacity in the science of pain, such as its intramural Methodologies Boot Camp. Also in 2011, NINR released a FOA to stimulate research that will link basic genomic discovery to the prevention and alleviation of symptoms in patients suffering from chronic disorders, while its intramural program is focused on studying the molecular-genetic mechanisms of pain and analgesia at the level of the individual. NCCAM recently funded two Centers of Excellence for Research on Complementary and Alternative Medicine to understand neural processing of chronic low-back pain using neuroimaging to elucidate how mind-and-body interventions affect these processes.

To coordinate, complement, and inform pain research goals and follow recommendations from the Institute of Medicine,[219] NIH has designated NINDS as the lead Institute for coordinating pain research efforts across the organization; selected a cadre of 11 Centers of Excellence for Pain Education; begun to develop new informational material for the public and medical professionals on pain conditions; and instituted more frequent meetings of the NIH Pain Consortium. NIH convened a number of conferences, workshops, and strategic planning efforts on chronic pain conditions in 2011–2012. For example, in April

[217] For more information, see http://painconsortium.nih.gov/CoEPES.html.
[218] For more information, see http://painconsortium.nih.gov/Headache-Research-Opp.pdf.
[219] For more information, see http://iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx.

2011, ORWH and the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group held a *State of the Knowledge Workshop on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research*. Also in April 2011, the *Pain Consortium's 6th Annual Symposium on Advances in Pain Research* was held on the NIH campus, entitled Mechanisms and Management of Overlapping Chronic Pain and Associated Conditions. In June 2011, NIDCR and other ICs sponsored the Sixth Scientific Meeting of the TMJ Association titled *Comorbid Chronic Pain Conditions – Mechanisms, Diagnosis and Treatments*. In September 2011, ORWH held a seminar and panel discussion on Sex Differences and Pain Research.

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. Challenges include basic research outcomes on chronic pain that poorly predict clinical applications of the research findings and pose as barriers to therapy development. Current animal models do not reflect the complexity of pain disorders, and assays for pain in animals and humans are not well matched. 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, as well as developing alternative pain medications with reduced abuse liability. For instance, NCCAM's Third Strategic Plan (2011–2015)[220] highlights its commitment to advancing understanding of pain and pain relief through complementary and integrative health approaches. NIDCR plans to invest in understanding the genomics of chronic orofacial pain, which often co-occurs with other chronic pain disorders, to better inform prevention, diagnosis, and treatment of pain disorders.

NIH's significant investment in pain research has recently provided important advances in our basic understanding of pain and our ability to treat it. For example, a gene variant discovered by NIH researchers protects some people from chronic pain after back surgery due to variations in signaling pathways. The team is now clinically testing an analgesic drug to target these signaling pathways.[221] NIH-funded research has identified a family of so-called Piezo proteins that are ion channel proteins essential to the sensation of painful touch and new therapeutic targets for the treatment of pain[222] and another study demonstrated that variations in the gene that encodes receptors for the hormone vasopressin are associated with pain sensitivity in a stress- and sex-specific manner in both mice and men.[223] NIH supported scientists have shown that transplantation of neuron precursors into adult spinal cord can reduce injury-induced neuropathic pain.[224] Finally, research has demonstrated that massage therapy helps reduce pain and improve function more rapidly than usual medical care in people with chronic low-back pain, according to a NIH-funded study published in the *Annals of Internal Medicine.*[225]

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[220] For more information, see http://nccam.nih.gov/about/plans/2011.
[221] For more information, see http://www.sciencedirect.com/science/article/pii/S1471489211002013
[222] For more information, see http://www.nature.com/nature/journal/vaop/ncurrent/full/nature10812.html
[223] Mogil JS, et al. *Nat Neurosci*. 2011;14(12):1569–73. PMID: 22019732.
[224] For more information, see http://www.cell.com/neuron/abstract/S0896-6273%2812%2900270-X?switch=standard
[225] Cherkin DC, et al. *Ann Intern Med*. 2011;155(1):1–9. PMID: 21727288.

As mentioned above, NINDS has been designated as the lead IC for pain research at NIH. In this role, the NINDS director, a longtime member of the Pain Consortium Executive Committee, has been appointed as the Chair of the committee, and will work to catalyze and coordinate enhanced trans-NIH research efforts on pain. As a reflection of this enhanced activity level, the Pain Consortium moved to a more frequent quarterly meeting schedule. The Interagency Pain Research Coordinating Committee was recently created under the Patient Protection and Affordable Care Act to enhance pain research efforts and promote collaboration across the government, advance fundamental understanding of pain, and improve pain-related treatment strategies.

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. It may be steady pain, or recurrent. It 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): pelvic pain strongly associated with the bladder and with urinary symptoms of frequency and urgency;
- Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): 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: chronic pain or discomfort of the vulva;
- Endometriosis: occurs when tissues that usually line a woman's uterus instead grow outside the uterus;
- Uterine fibroids: common, non-cancerous tumors that grow within and around the wall of the uterus; and
- Irritable bowel syndrome (IBS): a functional GI disorder whose symptoms 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 these conditions. IC/PBS, CP/CPPS, vulvodynia, and IBS are especially challenging pain conditions because their cause(s) are unknown, and fully effective treatments remain elusive.

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 NIDDK-led 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).[226]

Co-funded by ORWH, NIDDK leads the Interdisciplinary Research on Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) initiativeto support interdisciplinary research teams to address critical research questions focused on IC/PBS, with translational or clinical relevance. One team is exploring the possible role of the GI and/or reproductive tract microbiomes in IC/PBS,[227] the other is studying whether women with IC/PBS have global pain hypersensitivity.[228]

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-(SCOR) on Sex and Gender Factors Affecting Women's Health was established through an ORWH program and is co-funded by NIDDK and ORWH.[229]NIDDK is supporting the Rand IC Epidemiology (RICE) study and other large studies to answer fundamental questions about prevalence, potential causes, and risk factors of IC/PBS, and to learn more about the broader impact of this condition on health and quality of life.[230] The RICE study found through a nationwide telephone-based survey that 2.7 to 6.7 percent of adult women in the U.S. have symptoms consistent with IC/PBS.[231] The RICE study has also revealed a very high prevalence of sexual dysfunction among women with IC/PBS symptoms,[232] as well as high rates of depressive symptoms and panic disorder.[233] In addition to helping establish the public health burden, this information is important to the design of future clinical trials and epidemiological studies that can benefit people with IC/PBS.

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.

The NICHD-led *Pelvic Floor Disorders Network (PFDN)* 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.

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[226] For more information, see http://rt5.cceb.upenn.edu/mapp_web/MAPP_About.html.
[227] For more information, see http://projectreporter.nih.gov/project_info_description.cfm?aid=8257609&icde=10793568&ddparam=&ddvalue=&ddsub=.
[228] For more information, see http://projectreporter.nih.gov/project_info_description.cfm?aid=8257614&icde=10793568&ddparam=&ddvalue=&ddsub=.
[229] For more information, see http://www.cns.med.ucla.edu/CenterAbout.htm.
[230] Berry SH, et al. *J Urol*. 2011;186(2):540–4. PMID: 21683389.
[231] Berry SH, et al. *J Urol*. 2011;186(2):540–4. PMID: 21683389.
[232] Bogart LM, et al. *Urology.* 2011;77(3):576–80. PMID: 21215432.
[233] Watkins KE, et al. *Gen Hosp Psychiatry*. 2011;33(2):143–9. PMID: 21596207.

A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response, co-funded by NICHD and ORWH, addresses the efficacy of the drug gabapentin in vulvodynia treatment, and seeks to identify clinical features associated with successful treatment response.

NICHD funds the Prostaglandin E2 Signaling in Growth and Pains of Endometriosis study, co-funded by ORWH, aims to develop a new non-steroidal treatment for endometriosis, by examining the mechanisms by which inhibitors of specific prostaglandin receptors relieve endometriosis pain and prevent disease progression.

NIH also sponsors conferences to stimulate innovative research and encourage collaboration on pelvic pain disorders. On July 11–12, 2011, NICHD and ORWH co-sponsored the conference *Vulvodynia: A Chronic Pain Condition—Setting a Research Agenda* in Potomac, Maryland.[234] In November 2010, NICHD, ORWH, other NIH Institutes and Centers, and other federal Agencies sponsored *Advances in Uterine Leiomyoma Research: Third NIH International Congress*.

Brain function and anatomy in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) was revealed through fMRI. Results of this study show an association between functional and anatomical changes in the brains of men with CP/CPPS compared to those without this condition. Future studies will determine whether the observed brain changes are a result of chronic pelvic pain or represent risk factors for the development of CP/CPPS.[235]

Research on pelvic pain associated with UTIs has implicated bacterial LPS[236] in inciting pain through a novel mechanism involving host TLR4 receptors. This line of research is being explored by chronic urologic pelvic pain researchers as it also suggests that there may be an infectious origin in the persistent, chronic pain experienced by people with IC/PBS and CP/CPPS, and could yield new therapeutic strategies.[237]

A recent study in over 100 participants found that a cognitive behavioral therapy protocol for the treatment of IBS which directly targets visceral sensations may be particularly effective for this condition, compared to other CBT approaches not specifically focused on these sensations.[238]

Endometriosis 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, such as household chores, sexual

[234] For more information, see http://www.nichd.nih.gov/publications/pubs/upload/NIH_Vulvodynia_Plan_April2012.pdf
[235] Farmer MA, et al. *J Urol*. 2011;186(1):117–24. PMID: 21571326.
[236] Lipopolysaccharides (LPS) are found on the outer membrane of certain bacteria and elicit strong immune responses in animals.
[237] Rudick CN, et al. *J Infect Dis.* 2010;201(8):1240–9. PMID: 20225955.
[238] Craske MG, et al. *Behav Res Ther*. 2011;49(6-7):413–21. PMID: 21565328.

relations, sleep, exercise, and social activities. About 66 percent reported that their pain interfered with work. Most perceived a decrease in the quality of their work when suffering from endometriosis-related pain, and almost 20 percent reported being unable to work due to pain. 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. It can interfere with work performance and lead to significant absenteeism. These effects are costly to not only the patients, but also to the medical system and employers.[239]

Uterine fibroids, also called leiomyomas, are non-cancerous growths that occur in the wall of the uterus. They 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—have 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. Treatment options 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 a form of gene therapy that affects estrogen receptors. A recent study examined the safety and efficacy of this gene therapy in rats with uterine fibroids. Researchers randomized the rats to a fibroid gene therapy condition, an alternate gene therapy unrelated to fibroids, and a no treatment condition. Results revealed that the fibroid gene therapy shrunk fibroids by 45 percent at day 8 following the treatment and 80 percent at day 15. Treatment effects remained significant at day 30, with a 77 percent decrease in fibroid size compared to pretreatment size. In contrast, the two control groups saw fibroids double in size over the course of 30 days.

The gene therapy treatment was not only effective, it was safe. Tests revealed no damage to uterine tissue surrounding the fibroids or changes in liver function that might suggest toxicity. In most cases, the gene therapy did not appear to spread beyond the uterus, although some of the treated rats did show faint traces in the liver. This study provides preclinical data to support the development of gene therapy as an alternative to surgical and hormonal treatments of uterine fibroids.[240] NINR also developed a palliative care brochure, "Palliative Care: The Relief You Need When You're Experiencing the Symptoms of Serious Illness," to increase awareness of the many benefits of this comprehensive treatment among patient and caregiving populations, the general public, the media, and health care providers. The

[239] Fourquet J, et al. *Fertil Steril.* 2010;93(7):2424–8. PMID: 19926084.
[240] Hassan MH, et al. *Fertil Steril*. 2010;93(1):239–50. PMID: 19144333.

brochure was recently translated into Spanish, has been featured on the NIH website, and has been downloaded over 1,700,000 times from the NINR website since its release in September 2009.[241]

NIH will continue to pursue research avenues to alleviate the burden of chronic pelvic pain. NIDDK will maintain multidisciplinary research efforts to uncover the causes and contributors to IC/PBS, CP/CPPS, and IBS, and to develop prevention and treatment strategies. Current efforts should provide a foundation for improved methods to determine prevalence and identify affected individuals, and for the development and testing of new therapeutic strategies. The Institute will continue to collaborate and consult on new opportunities with NICHD and ORWH, and with members of the NIH Pain Consortium.

Obesity

Obesity[242] 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, 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.

Given the alarming rate of increase in obesity, NIH invests significantly in a broad portfolio of basic, clinical, and translational research to: 1) understand the complex factors that regulate body weight and that 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.

Basic research in obesity looks at numerous risk factors that may predispose an individual towards 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, such as brown fat; developmental exposure to a variety of environmental chemicals, such as arsenic and bispenol A; sex differences, as related to sleep, reproductive health, sex hormones, pregnancy, etc.; psychosocial and behavioral factors such as the role of social settings on food consumption; and environmental factors such as research on the effect of policies on food choices and how nutritional information and costs of health and unhealthy foods affect purchasing patterns.

Findings in basic research indicate potential new approaches toward combatting this rising epidemic. For example, studies have shown that high maternal glucose during pregnancy correlates with obesity risk in children, suggesting a potential avenue for intervention. Scientists have also found that disruption

[241] For more information, seehttps://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/palliative-care-brochure.pdf.
[242] An adult is considered to be obese when their body mass index exceeds 30 kg/m^2.

of circadian rhythms can lead to fat accumulation in the liver, increasing vulnerability to diabetes, obesity, and other metabolic problems.

Translational research in obesity capitalizes on these advances to provide new directions in preventing and treating obesity. For example, scientists have discovered a way to make white fat (common, subcutaneous fat) mimic the energy-burning properties of brown fat and muscle in rats.[243] Depletion of the neurotransmitter Neuropeptide Y in the brain resulted in active brown fat development and reduced body weight in rats, as well as protection from insulin resistance normally associated with a high fat diet.[244] In another study, researchers demonstrated that blockade of a specific receptor of endocannabinoids (chemicals that affect many processes, such as pain, memory, apetite, etc.) can lead to weight loss and reduced cardiovascular and metabolic risks in obese mice as well as in overweight or obese humans. However, this blockade may also result in negative psychiatric side effects due to blockade of these receptors in the brain. A novel receptor inhibitor that does not cross the blood-brain barrier was developed and tested in a mouse model of obesity, resulting in weight loss and other beneficial metabolic changes. Results suggest this class of receptor inhibitors may be effective for treatment of fatty liver disease due to obesity or heavy alcohol use.[245]

NIH invests significantly in clinical and postclinical research to address current obesity. Several of the intervention strategies being investigated focus on behavioral and environmental changes to foster healthier eating and physical activity, based in a variety of contexts, such as the home, schools, healthcare, and other community settings. Other strategies under study include medical or surgical interventions.

NIH-funded researchers are examining the benefits of lifestyle interventions for adults delivered in a variety of places, including community settings such as the YMCA, primary care clinics, faith-based sites, the workplace, and the internet. Study populations are drawn from urban and rural areas, may encompass state-wide populations, are sometimes gender specific, and include diverse race/ethnic groups.

Such studies are showing significant benefits. For example, researchers funded through NHBLI's Practice-Based Opportunity for Promotion of Weight Reduction program demonstrated that obese adults who received weight loss coaching via phone, online, and email contact, as well as support from their primary care providers, lost a significant amount of weight—5 percent or more of their starting body weight—and kept it off for two years.[246] In another study, lifestyle counseling sessions combined with the option to use weight loss medication or meal replacements, such as liquid shakes or meal bars, helped about one-third of obese participants lose a significant amount of weight and keep it off for two years.[247]

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[243] For more information, see http://www.nih.gov/news/health/jul2011/niddk-05.htm.
[244] Chao PT, et al. *Cell Metab.* 2011;13(5):573–83. PMID: 21531339.
[245] Tam J, et. al. *J Clin Invest*. 2010; 120(8):2953–66. PMID: 20664173.
[246] Appel LJ, et al. *N Engl J Med*. 2011;365(21):1959–68. PMID: 22085317.
[247] Wadden TA, et al. *N Engl J Med*. 2011;365(21):1969–79. PMID: 22082239.

The long-term effects of bariatric surgery are being examined through NIDDK's multi-center Longitudinal Assessment of Bariatric Surgery study. Scientists have recently found that gastric bypass surgery affects brain activation and reduces the desire to eat, particularly high-calorie foods.[248]

Many NIH ICs are investing in research to address the alarming rise of obesity in children and youth. Led by NCI with participation by many other ICs, 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. In 2011, NCCOR launched new online resources for researchers: the Catalogue of Surveillance Systems, which includes surveillance systems relevant to childhood obesity research and the evaluation of policy and environmental interventions, and the Measures Registry, a database of measures related to diet and physical activity.

Several ongoing trials seek to prevent or treat childhood obesity. For example, NIDDK and other ICs funded a new set of studies of lifestyle interventions ("LIFE-Moms") for overweight and obese pregnant women, designed to improve weight and metabolic outcomes for the women and their children. Four randomized trials are testing interventions to prevent excess weight gain in non-overweight youth and in those already overweight, and/or to reduce weight in obese and severely obese youth by targeting preschoolers, pre-adolescents, or adolescents. Other intervention strategies that focus on parents are also being explored, such as an intensive, family-based lifestyle intervention program for ethnically diverse children that was shown to result in sustained reductions in body weight and indicators of increased diabetes risk.[249]

A number of trials are addressing school-based interventions. For example, the NIDDK-supported HEALTHY study showed that an intervention in middle schools lowered the obesity rate in students at highest risk for type 2 diabetes (those who started out overweight or obese in sixth grade). However, schools that implemented the program did not differ from comparison schools in the overall prevalence of overweight/obesity.[250]

Researchers are examining community-level interventions. For example, the NHLBI-led Healthy Communities Study examines 275 communities and almost 24,000 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 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.

For older children and young adults, the Early Adult Reduction of Weight through Lifestyle intervention study includes six trials, led by NHLBI and including NICHD, that are testing behavioral approaches for weight control in young adults 18–35 years of age at high risk for weight gain, including pregnant and postpartum women, community college or university students, and young adults trying to quit smoking.

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[248] Ochner CN, et al. *Ann Surg.* 2011;253(3):502–7. PMID: 21169809.
[249] Savoye M, et al. *Pediatrics.* 2011;127(3):402–10. PMID: 21300674.
[250] HEALTHY Study Group, et al. *N Engl J Med*. 2010; 363(5):443–53. PMID: 20581420

Interventions are delivered using technologies such as smart phones, social networking sites, Bluetooth-enabled scales, and text messages.

Finally, multiple efforts are underway to communicate evidence-based approaches towards preventing and treating obesity. NHLBI, in collaboration with NIDDK, is updating the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Expert Panel Report*.[251] The panel is using a rigorous evidence-based approach and innovative information technology to identify, review, and evaluate the scientific evidence for specific research questions. 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 is collaborating with Home Box Office (HBO) on its Obesity Project, titled The Weight of the Nation, which was aired beginning in 2012. NIH staff has been providing scientific input to HBO on this project for several years. The CDC and Institute of Medicine (IOM) are also involved, with the IOM leading the coordination of the government partners. The multi-part documentary series will include four shows for adults, three shows for children (HBO family series), and supplemental films that will be posted on the HBO Web site. The project is funded with support from Kaiser Permanente and the Michael & Susan Dell Foundation.

NIH research on obesity is guided by the NIH Obesity Research Task Force. In 2011, the Task Force developed a new, 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 factors that contribute to obesity and its consequences
- 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

[251] For more information, see http://www.nhlbi.nih.gov/guidelines/obesity/obesity2/index.htm.

Allergy and Asthma

Allergic diseases, including asthma, currently are a major cause of illness and disability in the U.S. NIAID supports studies of the cause, pathogenesis, course of disease, and diagnosis of allergic diseases and evaluates new approaches to treat and prevent them.

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.[252] The coughing often occurs at night or early in the morning. NIAID supports targeted research to understand the causes of and develop preventions and treatments for asthma, a respiratory disease that affects almost 25 million Americans, including 7 million children aged 17 years and under. NIAID's research focuses on understanding how the environment, allergens, and genetics interact with the body's immune system to cause the disease and aggravate the symptoms.

Among recent advances, a NIAID-supported clinical trial showed that adding the antibody omalizumab, to the NIH guideline-based asthma treatment regimen of inner-city children significantly reduced their asthma symptoms and nearly eliminated seasonal asthma exacerbations. The study is being conducted through the NIH Inner-City Asthma Consortium launched in 2002 and is now composed of 10 academic clinical centers. The Consortium evaluates 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 studies to understand mechanisms underlying the onset and progression of asthma and research to develop diagnostic and prognostic biomarkers.

Food allergy is an abnormal response to a food, triggered by the body’s immune system. The response may be mild, or in rare cases it can be associated with the severe and life-threatening reaction called anaphylaxis. NIAID is the lead Institute at NIH for research in food allergy and supports research to help better understand, prevent, and manage this disorder that affects approximately 5 percent of children and 4 percent of adults in the United States. Since 2003, NIAID has substantially increased its support for food allergy research, which now spans the spectrum from basic research in allergy and immunology to clinical trials that are testing new strategies to treat and prevent food allergy

In recent years, concerns have mounted over the rise in prevalence of food allergy in children and adults. Currently, the only strategies to combat the condition are to avoid the particular food and treat the symptoms as they occur. In response to these concerns, NIAID collaborated with more than 30 professional organizations, federal agencies, and patient advocacy groups to develop clinical guidelines for use in the U.S. The guidelines will help healthcare professionals diagnose and manage non-life-threatening food allergies as well as anaphylaxis and other acute and potentially life-threatening food-allergy reactions. NIAID also supports development of approaches to treat or prevent food allergies. For example, an oral immunotherapy trial found that egg could be introduced safely into the diets of 75 percent of egg-allergic children.

[252] For more information, see http://www.nhlbi.nih.gov/health/health-topics/topics/cough/.

Digestive Diseases

Digestive diseases span a wide spectrum of diseases and disorders that affect the gastrointestinal (GI) tract, liver, gallbladder, and pancreas, many forms of which are chronic. Some digestive diseases are common, such as gastroesophageal reflux disease (GERD), while 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 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., irritable bowel syndrome under Chronic Pelvic Pain, inflammatory bowel diseases 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 in specific population groups, to identify the causes of diseases and how they progress, and to test new interventions for prevention and treatment of these costly diseases, including drugs, surgery, and behavior modification. 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 multi-center research efforts such as the Inflammatory Bowel Disease Genetics 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. The Institute 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.

Recent advances promise new approaches for treating and preventing these pervasive and debilitating disorders. A group of NIDDK-sponsored scientists has developed a method for turning human adult stem cells that are pluripotent (i.e., have the capability becoming different tissue cell type), into three-dimensional intestinal tissue in culture. This pioneering work has the potential to open up several new research directions, including elucidating pathways involved in inherited intestinal conditions, testing new drugs for their intestinal absorption, and even generating tissue for transplantation in conditions such as inflammatory bowel diseases, necrotizing enterocolitis, and short-gut syndromes.[253]

Researchers in NIDDK's Nonalcoholic Steatohepatitis Clinical Research Network have shown benefits of vitamin E as a treatment for nonalcoholic steatohepatitis (fatty liver disease) in adults, as well as in children with the most severe form of the disease. Nonalcoholic fatty liver disease is the most common chronic liver disease among U.S. children.[254] In other advances, NIDDK-sponsored investigators

[253] Spence JR, et al. *Nature*. 2010;470:105–9. PMID: 21151107.
[254] Sanyal AJ, et al. *NEJM*. 2010;362(18):1675–85. PMID: 20427778; Lavine JE, et al. *JAMA*. 2011;305(16):1659–68. PMID: 21521847.

successfully implanted physiologically functional, bioengineered anal sphincters in mice, which could lead to the development of a treatment for fecal incontinence in humans.[255] An NCCAM-supported trial showed that placebos administered with the patients' knowledge may be an effective treatment for IBS.[256] Researchers in the NIDDK Gastroparesis Clinical Research Consortium discovered evidence of changes at the cellular level in the stomachs of individuals with gastroparesis, a chronic condition characterized by impaired gastrointestinal motility, yielding new insights into this digestive disorder.[257]

NIH, along with Federal and non-Federal partners, will continue efforts to address goals for advancing digestive diseases research in the NIH-led National Commission on Digestive Diseases research plan.[258] For example, the NIDDK, together with NIAID, has established a new Intestinal Stem Cell Consortium, which is based on a research recommendation from the National Commission on Digestive Diseases' research plan, to stimulate basic research on the digestive system by developing new technologies to isolate, characterize, cultivate, and manipulate its 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 understanding of disease processes and to develop effective approaches to treatment. In 2012, the NIDDK entered into a cooperative research and development agreement (CRADA) with a pharmaceutical company to begin a clinical trial testing the safety and potential efficacy of a new treatment—cysteamine bitartrate—for nonalcoholic steatohepatitis (NASH) in children through the NASH Clinical Research Network.[259] The NIDDK also launched a Bowel Control Awareness Campaign to help patient and healthcare professionals feel more comfortable talking about conditions such as fecal incontinence.[260]

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 of function of these organs, due to a variety of causes, can result in life-threatening complications. 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.

NIH's basic and clinical research on kidney development and disease include research on the causes of kidney disease, the underlying mechanisms leading to progression of kidney disease to end-stage renal disease that requires replacement of kidney function through dialysis or transplantation, and the

[255] Raghavan S, et al. *Am J Physiol Gastrointest Liver Physiol*. 2010;299(2):G430–9. PMID: 20558766; Hashish M, et al. *J Pediatr Surg.* 2010;45(1):52–8. PMID: 20105579.
[256] Kaptchuk TJ, et al. *PLoS ONE*. 2010;5(12):e15591. PMID: 21203519.
[257] Grover M, et al. *Gastroenterology*. 2011;140(5):1575–1585. PMID: 21300066.
[258] For more information, see: http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/FinalResearchPlanPosting.htm.
[259] For more information, see http://www.nih.gov/news/health/jan2012/niddk-11.htm.
[260] For more information, see http://www.bowelcontrol.nih.gov/.

identification and testing of possible treatments to prevent development or halt progression of kidney disease. As the lead NIH IC for kidney disease, NIDDK supports studies of inherited diseases, such as polycystic kidney disease, congenital kidney disorders, and immune-related kidney diseases, including IgA nephropathy and hemolytic uremic syndrome. Focal Segmental Glomerulosclerosis (FSGS) is a cause of nephrotic syndrome in children and adolescents, as well as an important cause of kidney failure in adults and accounts for about a sixth of the cases of nephrotic syndrome.

NIDDK-supported clinical trials are exploring new treatment options and identifying novel links between kidney disease and its many co-morbid conditions, including cardiovascular disease. For example, NIDDK and NHLBI are co-sponsoring the Co-sponsored by NIDDK and NHLBI, the Chronic Renal Insufficiency Cohort Study[261] is evaluating long-term cardiovascular risk and outcomes of over 3,700 persons with chronic kidney disease. In a recent finding, scientists reported that high levels of FGF-23, a hormone that regulates phosphate metabolism, are associated with an increased risk of kidney failure and death among people with chronic kidney disease. 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.[262]

The Chronic Kidney Disease in Children Study[263] examines over 500 children with mild to moderately decreased kidney function in order to identify risk factors for further decrease in kidney function; closely monitor brain development; examine risk factors for heart disease; and look at the long-term effects of poor growth in this group.[264] [265] 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 Biomarker Consortium. NIDDK is also 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.[266]

NIA collaborates with NIDDK to support research on renal function and chronic kidney disease in aging. Projects include basic, clinical, and translational research on chronic kidney disease (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

[261] For more information, see http://porter.cceb.upenn.edu:7778/servlet/page?_pageid=55,138&_dad=portal30&_schema=PORTAL30.
[262] Isakova T, et al. *JAMA.* 2011;305(23):2432–9. PMID: 21673295.
[263] For more information, see http://statepi.jhsph.edu/ckid/.
[264] For more information, see http://healthcare.utah.edu/clinicaltrials/current/hemodialysis-fistula-maturation-hfm-study.html.
[265] For more information, see https://rarediseasesnetwork.epi.usf.edu/NEPTUNE/index.htm.
[266] For more information, see http://www2.niddk.nih.gov/Research/Resources/KidneyResources.htm.

development of CKD with advancing age; and/or diagnosis, medical management and clinical outcomes of CKD in this population.[267]

NIAID, along with NHLBI and NIDDK, supports the Clinical Trials in Organ Transplantation program[268] which aims to enhance the understanding of, 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,[269] 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[270], a clinical research consortium 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 (FSGS), 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 (HIVAN), 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 FSGS. These findings explain nearly all of the excess risk of non-diabetic kidney failure in African Americans. [271] Recently, *APOL1* variants have been shown in experiments to destroy trypanosomes that carry African sleeping sickness, a degenerative and potentially fatal disease affecting tens of thousands of people in sub-Saharan Africa.[272] In another study, the cellular distribution of *APOL1* was observed to differ in samples taken from normal kidneys compared to samples taken from patients with FSGS or HIV-associated kidney disease, most notably in a subset of smooth muscle cells that surround the arteries leading to the glomerulus. This observation suggests that a previously unrecognized problem with blood vessels may play an important role in kidney disease.[273]

In a clinical trial to treat FSGS in children and young adults, researchers found no difference between two different drug regimens to treat this form of kidney disease, which is stubbornly resistant to standard therapy. The trial was the largest clinical trial of pediatric and adult patients with steroid-resistant FSGS. The results of this investigation underscore the importance of continued research to identify new markers of disease progression (biomarkers) and other factors that contribute to this disease, which may provide new targets for therapy and allow physicians to more closely monitor a

[267] For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-165.html and http://grants.nih.gov/grants/guide/pa-files/PA-09-166.html.
[268] For more information, see https://www.ctotstudies.org/.
[269] For more information, see https://www.ctotc.org/.
[270] For more information, see http://www.immunetolerance.org/.
[271] Kao WH, et al. *Nat Genet*. 2008;40(10):1185–92. PMID: 18794854; Kopp JB, et al. *Nat Genet.* 2008;40(10):1175–84. PMID: 18794856. See also http://www.nih.gov/news/health/sep2008/niddk-14.htm.
[272] Genovese G, et al. *Science*. 2010;329(5993):841–5. PMID: 20647424.
[273] Madhavan SM, et al. *J Am Soc Nephrol.* 2011;22(11):2119–28. PMID: 21997392.

patient's response to treatment.[274] Scientists have identified a factor circulating in the blood of some patients with FSGS that may play an important role in the disease's initiation, progression, and recurrence. Levels of serum-soluble urokinase receptor were found to correlate with risk of FSGS and risk of recurrent FSGS following a kidney transplant. This discovery, once replicated by others, may have important implications both for research and for decisions regarding patient care.[275]

The Renin-Angiotensin-Aldosterone System (RAAS) is an endocrine system housed in the kidney and also expressed in other organs, including the heart and brain. RAAS plays an important role in the control of blood pressure (BP) and renal function. The first rat gene knockout model of RAAS was generated using a new technology called zinc-finger nucleases (ZFNs). The Ren-/- rat showed a greatly reduced blood pressure, having no plasma renin activity and no renin protein expressed in the juxtaglomerular cells in the kidney. The creation of a knockout rat will permit significant mechanistic research in this important system.[276]

In regard to public health information campaigns, NIDDK's *National Kidney Disease Education Program (NKDEP)*[277] 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.

NIDDK will continue its multi-faceted approach to research into kidney diseases, including:

- The continued fostering of basic research into the underlying biology of both normal kidney function and the mechanisms of disease initiation and progression.
- Clinical trials to explore novel treatment approaches for a wide variety of kidney diseases, as well as attempts to stabilize or reverse kidney disease in patients.
- Translational research to explore how best to move advances from the bench to the bedside, and from the bedside into clinical practice.
- Education and outreach campaigns to spread the evidence-based information about how people can prevent kidney disease and preserve kidney function.

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. Women are disproportionately affected by many urologic diseases and conditions, such as urinary incontinence, urinary tract infections (UTIs), and interstitial cystitis/painful bladder syndrome (IC/PBS) (see "Chronic Pelvic Pain"). A conservative estimate is that approximately 13

[274] Gipson DS, et al. *Kidney Int.* 2011;80(8):868–78. PMID: 21734640.
[275] Wei C, et al. *Nat Med.* 2011;17(8):952–60. PMID: 21804539.
[276] Moreno C, et al. *Hypertension.* 2011;57(3):614–9. PMID: 21242461.
[277] For more information, see http://nkdep.nih.gov/.

million Americans, most of them women, suffer from urinary incontinence. [278] 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 8 million doctor visits, nearly 7 million by women, in 2000, and many women suffer from frequent infections.[279] In men, non-cancerous growth of the prostate, or benign prostatic hyperplasia (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 to 60 to greater than 80 percent in men older than 80.[280] 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 can also contribute to or be the primary cause of sexual dysfunction. As people age, many non-cancerous 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.

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 BPH, urinary incontinence and UTIs. (Other disorders of the genitourinary tract, such as IC/PBS and chronic prostatitis/chronic pelvic pain syndrome, are discussed under "Chronic Pelvic Pain.") 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.

NIH efforts include the GenitoUrinary Development Molecular Anatomy Project, an NIDDK-funded consortium of laboratories working to provide the scientific and medical community with tools to facilitate research on the genitourinary tract.[281] With co-funding from ORWH, NIDDK also supports the Urinary Incontinence Treatment Network thatinvestigates surgical, behavioral, and medical treatments for stress and urge urinary incontinence.[282] One study in this network has revealed that two common operations for stress urinary incontinence (SUI) help women achieve similar levels of dryness. The Trial of Mid-Urethral Slings compared the outcomes of two minimally invasive surgical procedures involving use of synthetic mesh slings that are FDA-approved to treat this condition in women. Importantly, the trial also captured the risks and side effects of each type of surgery, which differed. Having this

[278] Urological Diseases in America. NIDDK, NIH Publication Number 07-5512. Available at http://kidney.niddk.nih.gov/statistics/uda/Urologic_Diseases_in_America.pdf
[279] Urological Diseases in America. NIDDK, NIH Publication Number 07-5512. Available at http://kidney.niddk.nih.gov/statistics/uda/Urologic_Diseases_in_America.pdf.
[280] For more information, see http://kidney.niddk.nih.gov/KUDiseases/pubs/kustats/index.aspx#16.
[281] For more information see: http://www.gudmap.org/
[282] For more information see: http://www.uitn.net/

information will better equip women with SUI and their doctors to weigh the benefits and risks of available treatment options.[283]

The NIDDK-supported multicenter, randomized, double-blind, placebo-controlled Randomized Intervention for Vesicoureteral Reflux trial is designed to determine whether daily antimicrobial prophylaxis is superior to placebo in preventing recurrence of UTI in children with vesicoureteral reflux.[284]

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 co-supported by NIDDK and ORWH have made tremendous progress in understanding factors in both the host organism (e.g., human or mouse) and the infecting bacteria that contribute to the onset and recurrence of UTIs.

An NIDDK-supported effort, Urologic Diseases in America (UDA) incorporates current and retrospective data on all aspects of the epidemiology, practice patterns, costs, and impact of urologic diseases in the United States. The UDA compendium delineates the changes in these areas over a ten-year period. In addition to updating the original 2007 compendium, the second phase of the UDA has focused less on descriptive analyses and more on analytical outcomes analyses, and attempted to increase involvement of the urologic community in analytical activities. The UDA is intended for use by public officials, nongovernment organizations, the media, academic researchers, health professionals, and the public.[285]

Results from the Complementary and Alternative Medicine for Urological Symptoms multi-center clinical trial, co-funded by NIDDK, NCCAM, and ODS, has found that the commonly used herbal dietary supplement saw palmetto does not improve BPH-related symptoms even at high doses—information that men with these symptoms and their health care providers can use in discussing and making choices about conventional and alternative therapies for symptom relief.[286]

Possessing a specific chemical coat called a K1 capsule appears to be a requirement for infectious bacteria to grow and form large masses called intracellular bacterial communities (IBCs) within the urinary tract of mice. Prior studies in rodent models indicated that formation of these IBCs helps promote sustained infection and may help explain at least some recurrent UTIs. By identifying the bacterial capsule as a factor that contributes to IBC formation, researchers have now illuminated targets for potential novel therapeutic interventions to prevent or treat UTIs. As IBCs have been observed in human bladder infections, these results likely have direct clinical implications.[287]

Kidney stones are among the most painful and most common urologic disorders. Scientists have uncovered new insights into how one particular type of kidney stone forms and grows, including a

[283] Richter HE, et al. *N Engl J Med.* 2010;362(2): 2066–76. PMID: 20479459,
[284] For more information see: http://www.cscc.unc.edu/rivur/
[285] For more information see: http://kidney.niddk.nih.gov/statistics/uda/
[286] Barry MJ, et al. *JAMA*. 2011;306(12):1344-51. PMID: 21954478.
[287] Anderson GG, et al. *Infect Immun*. 2010;78(3):963–75. PMID: 20086090.

possible strategy to disrupt this growth. This information may lead to better treatments for a condition that accounts for approximately 3 million visits to health care providers each year.[288]

Priority research areas identified by NIH include:

- Improving women's urologic health, including promoting the development of alternatives to antibiotic treatment for UTIs and finding new ways to prevent or treat urinary incontinence.
- Improving men's urologic health, including finding new ways to treat BPH and other diseases of the prostate.
- Attaining a better understanding of both the causes of lower urinary tract dysfunction (LUTD) and how treatments for LUTD symptoms intersect with patient reported outcomes and expectations so that treatments can be improved.
- Strengthening the pipeline of urologic research and researchers to ensure a next generation of effective treatment strategies for urologic diseases and conditions.

Diabetes

Type 1 Diabetes

Type 1 diabetes is an autoimmune disease that often strikes in infancy, childhood, or young adulthood. The NIDDK's landmark Diabetes Control and Complications Trial (DCCT), conducted from 1983 to 1993, showed that intensive glucose control dramatically delays or prevents the eye, nerve, and kidney complications of type 1 diabetes. 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, EDIC) showed that tight glucose control also prevents or delays the cardiovascular complications of type 1 diabetes. Because of improvements in treatment of the disease and new technologies, the long-term survival of those with type 1 diabetes has dramatically improved in the last 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. Major efforts to address type 1 diabetes—in particular those 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 three percent per year, suggesting that one or more unknown environmental factor is involved in triggering the disease. Type 1 diabetes is one of the few polygenic diseases for which over 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 has enabled the launch of prevention studies as well as studies to identify environmental trigger(s). Artificial pancreas technology—linking a continuous blood glucose

[288] Rimer JD, et al. *Science.* 2010; 330(6002):2066–-76. PMID: 20947757.

sensor and an insulin delivery system—has high potential to have a positive impact on patients' health and quality of life.

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 the artificial pancreas); 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 the NIDDK on behalf of the HHS Secretary and in collaboration with other NIH ICs.

Major research efforts include the 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 to slow progression of the disease in people who are newly diagnosed. Blood tests can accurately identify relatives of people with type 1 diabetes who are at high or moderate risk of developing the disease within five years. This has enabled *TrialNet* to launch clinical trials of promising prevention strategies, two of which (oral insulin, anti-CD3) are currently ongoing.[289] Recent results from three clinical trials testing agents targeting the immune system in people with new-onset type 1 diabetes reported that:

The drug abatacept slowed disease progression for 6–9 months compared to placebo. After that time, the effect of the drug diminished, and rate of loss of insulin production was similar in the abatacept and placebo groups. However, because of the initial beneficial effects, after two years, people in the abatacept group produced 59 percent more C-peptide, a marker of insulin production.[290] Preservation of C-peptide production is associated with better glucose control, less hypoglycemia, and reduced risk of complications. Another study showed that a Glutamic Acid Decarboxylase (GAD) vaccine had no effect after one year.[291] In type 1 diabetes, GAD is a major target of autoimmune response.

The drug rituximab, which destroys immune cells called B lymphocytes, preserved insulin production in newly diagnosed patients for 1 year, but the effect dissipated at 2 years. As drugs such as rituximab broadly deplete B lymphocytes, they can increase risk of infection and therefore have significant side effects. Nonetheless, the finding is important because it is propelling research to find drugs targeting the specific B lymphocytes involved in type 1 diabetes without the associated side effects.[292]

Research is showing that people with type 1 diabetes are living longer, healthier lives than ever before, largely due to long-term NIH supported research. The Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that, compared to conventional therapy, near-normal control of blood glucose—beginning soon after diagnosis of type 1 diabetes and continuing an average of 6.5 years—reduced the long-term risk (average 22-year follow-up) of developing kidney disease by 50

[289] For more information, see http://www.diabetestrialnet.org/.
[290] Orban T, et al. *Lancet.* 2011;378(9789):412–9. PMID: 21719096.
[291] Wherrett DK, et al. *Lancet.* 2011;378(9788):319–27. PMID: 21714999.
[292] Pescovitz MD, et al. *NEJM*. 2009; 361:2143–52. PMID: 19940299.

percent. The Diabetes Control and Complications Trial (DCCT) showed reduced biomarkers of complications. A decade after DCCT ended, EDIC found reduced heart attack, stroke, and cardiovascular death. Now, two decades later, EDIC found that early control reduced development of chronic and end stage kidney disease. 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.[293]

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 over 8,000 high-risk newborns and is collecting biosamples for analysis to identify potential triggers of type 1 diabetes. Children enrolled in the study are developing autoimmunity and type 1 diabetes at the predicted rates, indicating that those at risk can be accurately identified and that the study is on track to make a major contribution. Identification of an infectious agent that triggers autoimmunity could lead to a vaccine to protect against type 1 diabetes, or, if dietary factors are identified that protect from or contribute to the development of the disease, changes to infant feeding practices could be recommended. NIAID, NIEHS, and NICHD also participate in this study.[294]

The Beta Cell Biology Consortium (BCBC), led by NIDDK, is a consortium of researchers studying pancreas and beta cell biology and development toward a cell-based treatment for type 1 diabetes. BCBC investigators are working to reconstruct components of human type 1 diabetes in the mouse to observe how human diabetes develops, and then pinpoint the molecules, genes, and cells responsible.[295] Consortium researchers recently discovered that pancreatic glucagon-producing alpha cells could convert to insulin-producing beta cells in a mouse model of diabetes. This insight suggests that it may be possible to develop therapies to promote conversion of alpha cells to beta cells to restore insulin production in people with diabetes, and opens up intriguing new avenues for research toward cell replacement therapy.[296]

The Clinical Islet Transplantation Consortium, co-led by NIDDK and NIAID, is conducting clinical and mechanistic studies in islet transplantation, with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. The Consortium has completed enrollment of a pivotal (Phase III) islet transplantation trial (islet transplant alone), which is intended to support future FDA licensure of an islet product.[297]

To overcome the limitations of current insulin therapy, researchers have long sought to link glucose monitoring and insulin delivery by developing an artificial pancreas. There has been tremendous progress toward the development of an artificial pancreas that will mimic, as closely as possible, the way a healthy pancreas detects changes in blood glucose levels and responds automatically to secrete

[293] The DCCT/EDIC Research Group. *N Engl J Med.* 2011;365(25):2366–76. PMID: 22077236.
[294] For more information, see http://teddy.epi.usf.edu/.
[295] For more information, see https://www.betacell.org/.
[296] Thorel F, et al. *Nature*. 2010; 464: 1149–54. PMID: 20364121.
[297] For more information, see http://www.citisletstudy.org/.

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 a TrialNet study of whether initiation of closed-loop glucose control at diagnosis of type 1 diabetes and subsequent continuous glucose monitoring can preserve insulin production in people with newly diagnosed type 1 diabetes.[298] NIDDK is also supporting research training of engineers and behavioral scientists—fields that are critical for propelling progress in this area.

NICHD supports a diverse research portfolio related to type 1 diabetes in children and in pregnant women. For example, NICHD has funded research on the increased 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 and other areas of science. The Diabetes Research in Children Network, led by NICHD, is a research consortium investigating hypoglycemia and use of continuous glucose monitoring in children.[299]

The TRIGR clinical trial, led by NICHD, is examining whether hydrolyzed infant formula compared to standard cow's milk-based formula decreases the risk of developing type 1 diabetes in at-risk children.[300]

The Diabetic Retinopathy Clinical Research Network is an NEI-led, collaborative, nationwide network of eye doctors and investigators conducting multi-center 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 Hemoglobin A1C (HbA1C) Standardization Program, supported by CDC and NIDDK, is achieving international standardization and reliability in measurement of 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.[301]

NIDDK-supported research uncovered a key factor necessary for making insulin-producing beta cells in both humans and mice. Mice lacking the newly identified protein—called Rfx6—can make islets, but these islets do not contain insulin-producing cells. Interestingly, a rare form of neonatal diabetes is associated with mutations in the human gene that produces the Rfx6 protein, suggesting that Rfx6 plays a critical role in beta cell development in humans as well as mice. Researchers now know they will have

[298] For more information, see http://clinicaltrials.gov/ct2/show/NCT00891995?term=metabolic+control+in+new+onset+diabetes&rank=15.
[299] For more information, see http://www.nichd.nih.gov/research/supported/directnet.cfm.
[300] For more information, see http://www.nichd.nih.gov/research/supported/TRIGR.cfm.
[301] For more information, see http://www.ngsp.org/index.asp.

to ensure that Rfx6 is present in order to successfully generate beta cells from some other cell type for transplantation into people with diabetes.[302]

Researchers funded by NIDDK tested an implantable glucose sensor that monitors tissue glucose and reports data to an external wireless receiver. When implanted into pigs, the system functioned continuously for over a year. The implanted sensor also worked when tested for several months in diabetic pigs. These results are encouraging because an implantable device could potentially be used in the future as part of an artificial pancreas to automate glucose sensing and insulin delivery.[303]

NIDDK-supported scientists identified a novel genetic variant associated with type 1 diabetes risk that regulates a network of immune system genes.[304] Understanding genetic underpinnings of the disease could inform new targets for therapy.

NIDDK-supported scientists also discovered that a variant of an immune system molecule may contribute to type 1 diabetes by enabling an aberrant immune reaction against insulin. [305] This discovery could inform ways to intervene in the immune process to prevent type 1 diabetes or slow its progression.

Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee, published in February 2011, identifies compelling opportunities for research over the next decade on diabetes and its complications.

The over 8,000 participants being followed in TEDDY provide an unparalleled resource to study the development of the human microbiome from birth through childhood. Planned studies will build on research in mice to identify how interaction between the immune system and bacteria in the gut may alter the risk of type 1 diabetes.

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.

NIDDK is supporting a new study of the Joslin “medalists” – a population of people with type 1 diabetes who have survived with the disease for more than 50 years without serious development of eye, kidney, or nerve complications. The study seeks to identify factors that can protect against development of diabetes complications.

[302] Smith SB, et al. *Nature*. 2010. 463: 775–80. PMID: 20148032.
[303] Gough DA, et al. *Sci Transl Med*. 2010;2: 42ra53. PMID: 20668297.
[304] Heining M, et al. *Nature*. 2010; 467: 460–4. PMID: 20827270.
[305] Stadinski BD, et al. *Proc Natl Acad Sci USA*. 2010;107: 10978–83. PMID: 20534455.

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 (GDM), 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, but encompasses efforts by and collaborations with many other NIH Institutes and Centers and Offices, including NHLBI, NEI, NINR, NIEHS, NINDS, and ORWH.

Critical programs in type 2 diabetes include a new NIDDK-led consortium Optimizing Recovery and Preservation of Endogenous Insulin Secretion that is exploring approaches to slow beta cell loss in pre-diabetes and early in type 2 diabetes.[306] Another NIDDK-led consortium, the Multiethnic Study of Type 2 Diabetes Genes Consortium is working to identify genes or gene regions conferring type 2 diabetes risk in multiple ethnic groups.[307]

NIDDK's Translational Research for the Prevention and Control of Diabetes[308] and NIDDK Centers for Diabetes Translation Research fund type II translation 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. [309]

Major NIH clinical trials in people with type 2 diabetes include the Look AHEAD (Action for Health in Diabetes) trial. Led by NIDDK, with additional support from NHLBI, NINR, NIEHS, and ORWH, Look AHEAD is a multicenter randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through exercise and decreased caloric intake in overweight or obese adults with type 2 diabetes. The primary Look AHEAD outcome measure is cardiovascular disease events. The study is also examining effects on other diabetes complications, as well as co-morbid conditions such as depression.

This NIDDK leads TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth), a clinical trial that compared safety, efficacy, and cost-effectiveness of three different treatments for type 2

[306] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-10-013.html.
[307] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-004.html.
[308] For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html.
[309] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-10-009.html.

diabetes in youth. NIDDK also led the Diabetes Prevention Program Outcomes Study with additional support from NHLBI, ORWH, NIA, NICHD, and NEI. The Diabetes Prevention Program Outcomes Study is following participants in the landmark Diabetes Prevention Program to determine long term outcomes and durability of the DPP interventions. The Diabetes Prevention Program Outcomes Study has found that the lifestyle intervention continues to be effective for at least 10 years, and the study has also made numerous other important findings including the pharmacogenomic characterization of a gene influencing the transport and effectiveness of metformin, currently the most important medication in the treatment of type 2 diabetes. The study is also examining intervention effects on other health-related outcomes, including co-morbid conditions such as depression.

NHLBI leads an observational follow-up study (ACCORDIAN) of over 8,000 participants who were treated and followed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial is designed to further elucidate the long-term effects of the ACCORD interventions on cardiovascular disease (CVD) and type 2 diabetes outcomes. ACCORD was a large, randomized clinical trial in people with type 2 diabetes who were treated and followed for an average of approximately five years, through mid-2009. ACCORD tested the effects of three treatment strategies for control of glucose, blood pressure, and lipids on the rate of CVD events. The original trial found a modest decrease in the rate of non-fatal heart attacks and some indicators of eye and kidney disease, but there was a statistically significant increase in mortality in the intensive glycemia treatment group (targeting an Hba1c below 6.5 percent). The blood pressure and lipid interventions had no effect on CVD, but both the intensive blood sugar control and the lipid therapy reduced the progression of diabetic eye disease.

A planning grant has been funded by NIDDK to develop a major new trial Glycemic Reduction Approaches for Treating Diabetes: An Effectiveness Study, which will be designed to compare effectiveness of commonly used diabetes medications to determine the most effective treatment strategies for patients early in the course of their type 2 diabetes, with the aim of achieving and maintaining glycemic levels known to reduce long-term complications.

Other significant efforts include the NIEHS National Toxicology Program in which researchers are examining how to incorporate information on diabetes-related signaling pathways into the Tox21 framework for chemical screening. These efforts create an opportunity to use Tox21 approaches in a targeted testing framework to identify substances of concern, exposure to which may increase diabetes risk.

NIMH is supporting a randomized control trial enrolling persons with serious mental illness and comorbid diabetes from primary care safety net clinics. The psychosocial intervention, Targeted Training in Illness Management, involves nurses and peer educators—persons who have both a serious mental illness and diabetes and have been trained in illness self-management. These interventionists meet with patients in groups and model positive behavior change and the patient's active self-management to address both the mental disorder and diabetes in an integrated fashion. The intervention targets mental health and diabetes outcomes as well as overall functioning and quality of life.

Adverse Metabolic Side Effects of Second Generation Psychotropic Medications Leading to Obesity and Increased Diabetes Risk was a funding opportunity announcement (PA) issued jointly by NIMH and NIDDK to address the metabolic syndrome resulting from medications used by people with serious mental illness. Several innovative studies are underway. In addition, the first new therapy for diabetic retinopathy in 25 years was established in a trial demonstrating VEGF-inhibitor Lucentis is effective for slowing or reversing vision loss caused by diabetic retinopathy. Nearly 50 percent of patients who received the combination of Lucentis and laser treatment experienced substantial visual improvement after one year, compared with only 28 percent who received laser treatment alone.[310] The trial was conducted as part of the NEI and NIDDK co-funded Diabetic Retinopathy Clinical Trials Network.

Metabolomics (the study of chemical processes involving metabolites) revealed that plasma concentrations of five specific amino acids were strong predictors of future diabetes in a 12 year prospective study of 2,422 people with normal glucose levels. Testing for three of them—Ile, Phe, and Tyr—revealed a five- to seven-fold increase in type 2 diabetes likelihood between the top and bottom quartiles.[311]

Diabetes Prevention Program (DPP) participants homozygous for the most common allele of an *SLC47A1* SNP (roughly a third of the population) received no diabetes-prevention benefit from metformin, although the metformin arm of the study developed diabetes 31 percent less often than those taking placebo. This could represent a major new advance for personalized medicine, as a test could identify which of millions of Americans with prediabetes would likely benefit from metformin.[312]

The peptide hormone FGF19, produced by cells of the distal small intestine in response to the presence of bile salts, signals to the liver to complete the task of storing glucose as glycogen. It is therefore an important regulator of blood glucose levels, and because it acts through a different pathway than insulin, stimulation of its effectors may be a valuable new approach to type 2 diabetes treatment.[313] Other studies have shown that in response to glucagon, the class IIa histone deacetylases (HDACs) activate FOXO to stimulate liver glucose production. Experimentally limiting HDAC activity in the livers of mice with type 2 diabetes helps normalize blood glucose, suggesting another potential route for type 2 diabetes therapy.[314]

A high-fat diet can interfere with the post-translational modification of the glucose transporter in pancreatic beta cells of mice, so an insufficient supply of the protein reaches the cell surface to detect increases in glucose levels. Mature, membrane-embedded transporter was also reduced in beta cells

[310] Elman M, et al. *Ophthalmology*. 2010;117 (6):1064–77. PMID: 20427088.
[311] Wang TJ, et al. *Nat Med*. 2011;17(4):448–53. PMID: 21423183.
[312] Jablonski KA. *Diabetes*. 2010;59(10):2672–81. PMID: 20682687.
[313] Kri S, et al. *Science*. 2011;331(6024):1621–4. PMID: 21436455. Potthoff MJ, et al. *Cell Metab*. 2011;13(6):729–38. PMID: 21641554.
[314] Wang B, et al. *Cell*. 2011;145(4):596–606. PMID: 21565616. Mihaylova MM, et al. *Cell*. 2011;145(4):607–21. PMID: 21565617.

from type 2 diabetes patients. This suggests insufficient beta cell insulin production could precede or occur in tandem with peripheral insulin resistance, leading to type 2 diabetes.[315]

A compound was found that binds PPAR-γ[316] and inhibits its phosphorylation without broadly simulating it. In mice, a new compound was found that improved insulin sensitivity without causing the side effects observed in treatment with currently approved medicines that work via the same mechanism.[317] A Phase I clinical trial with the compound has begun.[318]

Vitamin D supplementation was found to improve insulin sensitivity in a 16-week clinical trial of people with prediabetes.[319] A planning grant has been funded for a larger, longer-term randomized clinical trial, the Vitamin D for Type 2 Diabetes (D2D) trial. Although diabetes is a known risk factor for periodontal disease, new findings show that people with prediabetes are also at significantly elevated risk for periodontal disease.[320] An observational study of over 65,000 women aged 50 to 75 found that not only does diabetes increase the risk for depression, but also depression increases the risk for type 2 diabetes.[321]

NIMH and NIDDK recently co-funded a landmark study to improve care for patients with both depression and diabetes. The researchers examined a primary care approach called TEAMCare in which nurses worked with patients and their physicians to manage care for depression and poorly controlled diabetes in an integrated fashion, using evidence-based care guidelines. The study found that TEAMCare patients experienced less depression, better control of blood sugar, improved quality of life, and higher satisfaction with care, as compared to patients receiving usual care.[322]

In addition to research efforts, the National Diabetes Education Program, a joint effort of NIDDK and the Centers for Disease Control and Prevention, translates the latest science and spreads the word that diabetes is serious, common, and costly, yet controllable and, for type 2 diabetes, preventable. The ORWH contributes funding for the NDEP's GDM awareness campaign, "It's Never Too Early to Prevent Diabetes," an effort to inform women with a history of GDM, their families, and health care providers of the increased risk for future type 2 diabetes in both mothers and babies affected by GDM, and steps they can take to reduce this risk.

The February 2011 report titled *Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee*, spearheaded by NIDDK,

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[315] Ohtsubo K, et al. *Nat Med*. 2011;17(9):1067–75. PMID: 21841783.
[316] Peroxisome proliferator-activated receptor gamma (PPAR-γ) regulates glucose metabolism and fatty acid storage.
[317] Choi JH, et al. *Nature*. 2011;477(7365):477–81. PMID: 21892191.
[318] Lee JM, et al. *Nature.* 2011;474(7352):506–10. PMID: 21614002.
[319] Mitri J, et al. *Am J Clin Nutr.* 2011;94(2):486–94. PMID: 21715514.
[320] Choi YH, et al. *Diabetes Care*. 2011;34(2):381–6. PMID: 21216848.
[321] Pan A, et al. *Arch Intern Med*. 2010;170(21):1884–91. PMID: 21098346.
[322] Katon WJ, et al. *N Engl J Med*. 2010;363(27):2611–20. PMID: 21190455. See also: http://www.nimh.nih.gov/science-news/2010/case-managed-care-improves-outcomes-for-depressed-patients-with-multiple-medical-conditions.shtml.

identifies compelling opportunities for NIH-supported research over the next decade on diabetes and its complications. Key type 2 diabetes research priorities include:

- Genetics. Type 2 diabetes, obesity, and their complications have strong genetic bases that interact with environmental and behavioral factors. Identifying those factors that influence disease susceptibility or response to various therapies is a vital approach for developing new strategies for prevention and treatment of diabetes.

- Comparative effectiveness research. There are now a significant number of medications available for treatment of type 2 diabetes, and research is needed to determine which drug should be added when initial therapy with the first line therapeutic (generic metformin) is inadequate to control glucose. This subject is the focus of Glycemic Reduction Approaches for Treating Diabetes, a study now receiving pre-trial planning funds.

- Preserving islet function in type 2 diabetes. Researchers will study whether early, aggressive medical treatment of type 2 diabetes helps to stem the course of beta cell loss typically observed in the disease.

- Complications. In addition to beta cell failure, type 2 diabetes is marked by metabolic abnormalities in multiple organ and tissue systems, including muscle, liver, fat, and also the brain; diabetes is a risk factor for Alzheimer's disease. Research is needed to understand these connections.

- Systems biology. A systems biology approach could provide an unprecedented depth of understanding of the disease variability observed in people with type 2 diabetes and help identify pathways of disease development and progression. Research goals in this area integrate many different areas of type 2 diabetes research to achieve a comprehensive portrait of the disease.

- Obesity research. Stemming the rising tide of type 2 diabetes will require research to understand the causes of obesity and weight gain, their link to type 2 diabetes, and development of prevention and treatment strategies.

- Special populations. Developing tailored approaches to diabetes treatment and prevention would reduce the burden of disease in specific populations, including children, older adults, pregnant women, people with other serious diseases and conditions, and minority populations that are disproportionately affected by diabetes.

- Translational research. A key challenge in diabetes research is translating the important findings of controlled clinical trials for diabetes prevention or treatment into approaches that are effective, affordable, safe, and sustainable in real world settings. Research goals in this area are aimed at designing diabetes interventions to work in different populations and individuals and within discrete systems of care.

Following the landmark two-year diabetic macular edema (DME) trial[323] that demonstrated that intravitreal injection of VEGF-inhibitor Lucentis (ranibizumab) with prompt or deferred laser treatment was superior to the standard therapy of laser alone, the NIH-funded Diabetic Retinopathy Clinical Research Network is launching a comparative effectiveness trial of Lucentis versus Avastin. Avastin, a similar yet significantly less expensive drug also produced by Genentech/Roche, has been used off-label for DME, but data on its effectiveness for this indication is not available, although a recent head-to-head trial (Comparison of AMD Treatment Trial) in a different eye disease, macular degeneration found the drugs to be equally effective for visual acuity.[324]

Substance Abuse and Addiction

Nearly four decades of research supported by NIH have proven addiction to be a complex brain disease characterized by compulsive, at times uncontrollable, drug 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 behavior, reflecting the compulsive nature of this disease. In fact, many of the drug-induced brain adaptations can be long lasting, which is, in part, why addiction is considered a chronic disease. And like the more classic chronic diseases (e.g., diabetes, hypertension, and heart disease), most addicted patients require long-term treatment, and relapse (or symptom re-emergence) may occur during the treatment or recovery process.[325]

NIDA's and NIAAA's diverse research portfolios, reflected in their strategic plans,[326] are geared toward preventing the initiation of drug and alcohol use and their escalation to addiction; developing successful treatments for drug and alcohol abuse and addiction; and improving treatment accessibility and implementation. NCI also supports research in this area, particularly with regard to smoking cessation and tobacco control. In addition, research on the cycle of substance abuse naturally extends to the critical research needed to address the medical (e.g., HIV, fetal alcohol syndrome), social, and legal consequences of both substance use in the short-term, and the disease of addiction.

Research on the prevention of substance abuse and addiction includes research on genetics, development, and basic neurobiology, as well as the effects of environment and social/policy interventions on the risk of drug and alcohol use initiation and its transition to addiction. Large-scale epidemiological studies (over 40,000 respondents in a data collection cycle) 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 (NESARC) provide information on substance use and co-occurring conditions that can help to inform prevention efforts to target the areas and populations of greatest concern.

In terms of genetics, research shows that about half 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

[323] Elman MJ, et al. *Ophthalmology.* 2011;118(4):609–14. PMID: 21459214.
[324] Martin D, et al. *Ophthalmology.* 2012;119(7):1388–98. PMID: 22555112.
[325] See *Drugs, Brains, and Behavior, The Science of Addiction*: http://www.drugabuse.gov/publications/science-addiction.
[326] For more information, see http://www.drugabuse.gov/about-nida/2010-strategic-plan and http://www.niaaa.nih.gov/AboutNIAAA/Interagency/Pages/progressreport.aspx.

the individual genes that affect risk for substance use and addiction can help tailor 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. 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).

NIDA is supporting research designed to uncover neural correlates of risk and protection that influence brain development and substance use trajectories. For example, using functional magnetic resonance imaging (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 addiction.

Abuse of prescriptions drugs, primarily opiate pain medications, ranks second (after marijuana) among illicit drug users. Notably, unintentional poisoning deaths involving prescription pain relievers has more than quadrupled from 1999 through 2009 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 reduce the need for highly addictive opioid medications, along with their availability for diversion and abuse.

Early identification of young people at risk for drug and alcohol use as well as identification of those already drinking or using drugs are key to the prevention of more serious problems later. NIDA and NIAAA will continue to support research evaluating the effectiveness of screening, brief intervention, and referral (SBIRT) for alcohol and other drug use in pediatric and primary care settings. In 2011, NIAAA released a simple, easy-to-use, developmentally appropriate, and empirically based alcohol screening guide.[327] This guide is helping health care practitioners identify children at elevated risk for using alcohol as well as those children and adolescents who have already experimented or are more heavily involved with alcohol.

NIH research is also focused on reducing college drinking and drug abuse and their many social and health consequences, including cognitive impairment, poor academic performance, assault, drug and alcohol poisoning, injuries, drunk and drugged driving, addiction, and even death from overdose.

[327] For more information, see http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/YouthGuide.

Research encompasses epidemiological surveys of college populations, as well as individual and environmental approaches to reducing substance use and associated consequences.

Treatment approaches under investigation include research on development of medication and behavioral treatments, screening, and intervention practices, as well as comparative research to evaluate the effectiveness of treatment strategies for addiction.

Despite the enormous burden that drug abuse and addiction exact on our society, few medications are yet approved to treat substance use disorders. This disconnect has made the development of medications a top priority for NIDA. NIDA's strategy in this regard has been to "de-risk" compounds so that they can become attractive to the pharmaceutical industry. To accelerate clinical trials for 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, supported using ARRA funds. Probuphine is a buprenorphine medication implanted under the skin, which allows continuous medication delivery for six months after a single treatment that is expected to improve adherence and reduce the possibility of diversion. Another strategy is a novel public-private partnership to develop, test, and bring to market safe and effective anti-smoking medications. NIAAA has made substantial progress in testing potential new medications for alcohol dependence. The inclusion of DNA collection and analysis as part of clinical trials makes it possible to move treatment for alcohol dependence closer to personalized medicine.

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 have also 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. Finally, NIDA is supporting 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.

Recognizing that only a small percentage of individuals with alcohol or drug abuse and addiction problems seek help, NIDA and NIAAA are facilitating the implementation of substance abuse screening and brief intervention into the primary healthcare setting. In addition to its youth screening guide, NIAAA has developed and disseminated its *Clinician's Guide: Helping Patients Who Drink Too Much*[328] that provides standard guidelines for SBIRT in primary care and mental health settings. Through the NIDAMED initiative[329]—NIDA's outreach to practicing physicians, physicians in training, and other

[328] See NIAAA Clinician's Guide: Helping Patients Who Drink Too Much, http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/Pages/guide.aspx.
[329] For more information, see http://www.drugabuse.gov/medical-health-professionals.

health professionals—NIDA continues to encourage physician screening of tobacco, alcohol, and illicit and 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 patient drug use, followed by the NIDA-Modified Alcohol, Smoking, 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.

NIDA's portfolio includes a significant investment in effectiveness and comparative effectiveness research that encompasses community treatment programs as well as the criminal 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. NIDA is taking a similar approach to enhance treatment for drug-addicted individuals within the criminal justice system through its Criminal Justice-Drug Abuse Treatment Studies network, an inter-agency collaboration aimed at bringing proven treatment models into the criminal justice system to help stop the vicious cycle of drug abuse and crime.

The study of the medical and social consequences of drug abuse and addiction requires a considerable continuing scientific investment in several areas. HIV/AIDS remains one of the most serious medical consequences of drug abuse, and its link goes well beyond injection drug use, because intoxication or addiction often leads to impaired decision making and/or risky sexual behaviors. Thus, NIDA supports research to improve HIV prevention among drug abusers, enhance screening and treatment access for HIV/AIDS and other co-occurring conditions, as well as uncovering and preventing any potential interactions between drugs of abuse, HIV/AIDS disease processes, and the medications used to treat both. For example, extensive research has demonstrated that drug abuse treatment is HIV prevention. 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 create the infrastructure and linkages needed to implement the "Seek, Test, Treat, and Retain" strategy, which *seek*s out high-risk, hard-to-reach vulnerable populations (e.g. substance abusers), *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, abuse, 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. In 2008, alcoholic liver disease was responsible for nearly 1 in 5 liver transplants in the U.S. NIAAA continues to support research on the underlying mechanisms of alcohol induced tissue and organ damage to identify potential targets for treatment, inform strategies to prevent damage and improve the prognosis for alcohol-related liver disease.

Given the prevalence of drinking, especially binge drinking among adolescents, the association between early alcohol use and later alcohol dependence, and other concerns about the effects of alcohol on the developing brain, NIAAA has funded a combination of human and animal studies to better understand how alcohol affects adolescent brain development and function.

Exemplary recent advances in addiction science include the development of a nicotine vaccine. Although studies have demonstrated proof of concept for nicotine vaccines, the vaccines' inability to generate a sufficiently strong immune response has hindered their success. A 2011 winner of NIDA's Translational Medications Avant-Garde Award is developing and testing a novel vaccine that induces a strong immune response against nicotine without the need for chemical enhancers. This innovation could result in a less expensive vaccine with fewer side effects. The vaccine will be administered intranasally, and is expected to enter clinical trials within the next five years.

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.[330]

A cost-benefit analysis of the Communities That Care (CTC) 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.[331]

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 through a chemical process called hydrolysis. Researchers have previously created BChE-based compounds with enhanced cocaine-metabolizing properties and have now extended their effectiveness though use of a virus (modified with the DNA for producing the cocaine-metabolizing enzyme) as a delivery method. Over a 6-month period, cocaine-dependent animals injected with the DNA-modified virus 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. Using a viral delivery system for a cocaine-metabolizing enzyme shows promise as a way to prevent relapse in cocaine addiction, particularly if combined with cocaine vaccines currently under study.[332]

[330] Jones HE, et al. *N Engl J Med.* 2010;363(24):2320–31. PMID: 21142534.
[331] Hawkins JD, et al. *Arch Pediatr Adolesc Med.* 2012;166(2):141–8. PMID: 21969362.
[332] Anker JJ, et al. *Biol Psychiatry*. 2012;71(8):700–5. PMID: 22209637.

Most studies examining treatments for opioid dependence have been conducted with heroin-addicted patients at methadone clinics, so little data exist on treatment for patients addicted to prescription pain relievers, especially treatment delivered in the offices of primary care doctors. To help address this issue, NIDA's Clinical Trials Network launched the Prescription Opioid Addiction Treatment Study in 2007, which took place at 10 treatment sites around the country. In the study, more than 600 treatment-seeking outpatients addicted to prescription opioids received Suboxone (buprenorphine plus naloxone) in combination with substance abuse counseling sessions or brief standard medical management, in which physicians evaluated treatment effectiveness and recommended abstinence and self-help participation. While no difference occurred relative to the behavioral treatments, approximately 49 percent of participants reduced prescription pain reliever abuse during Suboxone treatment. However, this success rate dropped to 8.6 percent once the Suboxone was discontinued, indicating that medication maintenance is indicated for this population and that more research is needed to determine the required duration.[333]

NIAAA supported a study to determine if the medication ondansetron, which blocks the transporter for the neurotransmitter serotonin, could reduce problem drinking in alcohol-dependent individuals. Ondansetron is currently used to treat nausea and vomiting, often following chemotherapy. Variants in the gene encoding the serotonin transporter, designated as LL and TT, were previously shown to be associated with heavy drinking. The study showed that subjects with the LL genotype who received ondansetron reduced their average number of daily drinks and had significantly more days of abstinence, relative to those who received placebo. Ondansetron's effects were even more pronounced among individuals who possessed both the LL and TT gene variants, while subjects who lacked the LL variant showed no improvement with ondansetron.[334]

The accumulated scientific knowledge derived from these studies and many many others will be used to transform the way addiction is treated and how to prevent drug abuse or its escalation to addiction. Some exciting initiatives include:

- NIDA is interested in harnessing complete genome and "deep" sequencing capabilities to uncover genetic information at the highest level of detail to help expose rare genetic variants associated with addiction. Other areas of interest include genotype-driven deep phenotyping (i.e., the characterization and systematic cataloging of biological and behavioral traits relevant to substance abuse and addiction risk and trajectories) to determine how a particular genetic variation alters neural and brain function to contribute to an addiction-related phenotype.

- The above techniques are beginning to merge with a growing portfolio of epigenetic initiatives to explain how environmental factors (e.g., chronic stress), biological processes (e.g., brain development) and exposure to various neurological insults (e.g., exposure to drugs of abuse) can alter the expression of specific genes that influence brain organization and function and how this in turn protects or facilitates expression of substance use disorders. Recent studies reveal

[333] Weiss RD, et al. *Contemp Clin Trials*. 2010;31(2):189-99. PMID: 20116457.
[334] Johnson BA, et al. *Am J Psychiatry*. 2011;168(3):265-75. PMID: 21247998.

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.

- NIDA will capitalize on our expanded knowledge of 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). Medications will also be developed to affect systems common to multiple addictions, such as stress-induced relapse or cognitive remediation.

- NIH Competitive Revision Applications for Research Relevant to the Family Smoking Prevention and Tobacco Control Act is a joint NIH/FDA initiative supporting research investigating the toxicity and use of new and emerging tobacco products; effective methods to substantially reduce the toxicity of tobacco products and smoke; effective methods to reduce the overall addictiveness of cigarettes and other tobacco products; and consumer perceptions and behaviors related to tobacco products, claims, and communications about tobacco products.

NIAAA's Strategic Plan[335] includes a focuses on a wide range areas. The following are a few examples:

- NIAAA will continue to pursue personalized medicine by focusing on treatment strategies that better match patients to medications that produce the greatest benefit with the least adverse side effects and that are based on patient pharmacogenomic profiles and other characteristics. Pharmacogenomics research will also inform studies of new medications for the treatment of alcohol use disorders.

- NIAAA has launched its new National Health and Alcohol Study, which, like its predecessor NESARC, is a nationally representative survey of over 40,000 participants. NHAS has added a DNA collection component to enhance understanding of how genes and environment influence the development and course of both alcohol use and co-occurring disorders.

- A new funding opportunity announcement will promote research on 1) how chronic and acute alcohol consumption affect behavioral regulation processes at the epigenetic, cellular, systems (neurocircuitry), and behavioral levels; 2) how these effects lead to the propensity to develop alcohol dependence; and 3) the influence of genetic and environmental factors on behavioral regulation processes contributing to alcoholism risk.

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. Early disease is characterized by yellow deposits under the retina called drusen. Advanced disease has two forms. 'Dry' AMD, also called geographic atrophy (GA), occurs when the retinal pigment epithelium (RPE) and then the photoreceptors in the macula slowly break down, gradually blurring central vision in affected eyes. Exudative, or 'wet', AMD is marked by choroidal

[335] For more information, see http://pubs.niaaa.nih.gov/publications/StrategicPlan/NIAAASTRATEGICPLAN.htm.

neovascularization (CNV) in which abnormal blood vessels growing under the retina leak blood and fluid, thereby destroying the structure of the macula and leading to loss of photoreceptors. More than 85 percent of all people with intermediate and advanced AMD combined have dry AMD. However, if only advanced AMD is considered, about two-thirds of patients have wet neovascular AMD. Because almost all vision loss comes from advanced AMD, the wet form leads to significantly more vision loss than the dry form.

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. According to 2004 published data on prevalence of AMD, of the nearly 60 million people in the United States age 55 or older in the year 2000, an estimated 7.3 million are at risk of developing advanced, sight-threatening AMD in one or both eyes and 1.75 million citizens currently have AMD. This number is expected to increase to nearly 3 million by the year 2020.[336]

The landmark Age-Related Eye Disease Study (AREDS) is a longitudinal treatment trial and natural history study established that at-risk AMD patients taking high levels of antioxidants and zinc could reduce progression to advanced disease by 25 percent. Building on these findings, AREDS2 is a multi-center clinical trial examining oral supplementation of macular xanthophylls (lutein and zeaxanthin) and/or long-chain omega-3 fatty acids on the progression to advanced AMD and cataracts. AREDS2 is also evaluating effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression. Results from this large, multicenter clinical trial are anticipated in 2013.

The *VIT*amin D and Omeg*A*-3 Tria*L* , the Low Vision Depression Trial, is an interventional trial to test collaborative care between eye care professionals and low vision occupational therapists to prevent or reduce depression that accompanies AMD.

In May 2011, first-year results from the two-year Comparison of AMD Treatment Trials (CATT) found Avastin, a drug approved to treat some cancers and that is commonly used off-label to treat wet AMD, is virtually identical in improving visual acuity as the Food and Drug Administration-approved drug Lucentis[337]. The four-armed CER trial also demonstrated excellent results for both drugs when compared between two dosing schedules, either monthly, or on an as needed basis, determined by monitoring signs of fluid in the retina. Both drugs are anti-VEGF[338] compounds manufactured by Genentech. Serious adverse events (primarily hospitalizations) occurred at a 24 percent rate for patients receiving Avastin and a 19 percent rate for patients receiving Lucentis. These events were distributed across many different conditions, most of which were not associated with Avastin in cancer clinical trials where the drug was administered at 500 times the dose used for AMD. The number of deaths, heart attacks, and strokes were low and similar for both drugs during the study. The median age of patients in CATT was

[336] Friedman DS, et al. *Arch Ophthalmol*. 2004;122(4):564–72. PMID: 15078675.
[337] Martin D, et al. *NEJM.* 2011;364:1897–908. PMID: 21526923.
[338] Vascular Endothelial Growth Factor (VEGF) is a signal protein that stimulates the process of forming new blood vessels from endothelial cells and growing new blood vessels from pre-existing vessels.

over 80 years, and a high rate of hospitalizations might be anticipated as a result of chronic or acute medical conditions more common to older populations. Importantly, CATT was not powered to determine whether there is a significant difference in adverse event rates between the two drugs.[339]

Two large AMD GWAS studies (18,000 subjects) identified three new genes associated with AMD; two of these genes (hepatic lipase gene and cholesterylester transfer protein) are involved with high-density lipoprotein cholesterol metabolism, implicating a new biochemical pathway involved in the pathogenesis of AMD. Weaker associations were found with other genes in the cholesterol pathway: ATP-binding cassette transporter and lipoprotein lipase. The studies also identified a new strong association on chromosome 22, near metalloproteinase inhibitor 3 (TIMP3). Mutations in TIMP3 had been known to cause Sorsby's fundus dystrophy, a rare, inherited early-onset form of macular degeneration.[340] [341]

In patients with dry AMD or geographic atrophy, researchers discovered that a deficiency of the Dicer1 enzyme in retinal pigment epithelial cells was associated with cell death of these cells. Dry AMD happens when the light-sensitive cells in the macula slowly break down, gradually blurring central vision in the affected eye. In the absence of the Dicer enzyme, cell death was linked to toxic accumulation of double-stranded *Alu* RNA. Increasing the level of Dicer or interfering with *Alu* RNA rescued the cell death, suggesting potential therapies for dry AMD.[342]

Investigators studying choroidal neovascularization, the creation of new blood vessels in parts of the eye, in human patients with wet AMD discovered that the protein CCR3 is expressed in choroidal cells (cells in the layer of the eye that contains connective tissue and lying between the retina and the sclera). Wet AMD happens when abnormal blood vessels behind the retina start to grow under the macula. These new blood vessels can be fragile and leak blood and fluid. The blood and fluid cause the macula to swell and damage occurs rapidly. The damage may also cause scarring of the retina. However, CCR3 is not expressed in disease-free subjects, or from early stage AMD patients who do not yet demonstrate choroidal neovascularization (i.e., patients with dry AMD). Therefore, CCR3 may serve as a biomarker for detecting choroidal neovascularization in patients at early stages of AMD before vision loss occurs. It also may serve as a therapeutic target: drugs that block CCR3 prevented additional vessel growth in tissue removed from AMD patients with choroidal neovascularization, or in animal models.[343] NIH is also funding research to understand the genes that control angiogenesis (the growth of new blood vessels from preexisting blood vessels) in AMD, as such work could open up new research and therapeutic opportunities.[344] In addition, newly discovered pathways implicated in AMD genetics studies include growth factors, inflammation (Complement Factor H), and cholesterol. NEI with NIDDK is planning a workshop on diagnostic and therapeutic potential CFH pathway in the hope of stimulating new research areas.

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[339] Martin D, et al. *Ophthalmology.* 2012;119(7):1388–98. PMID: 22555112.
[340] Neale BM, et al. *PNAS.* 2010;107(16):7395–400. PMID: 20385826.
[341] Chen W, et al. *PNAS.* 2010;107(16):7401–6. PMID: 20385819.
[342] Kaneko H, et al. *Nature.* 2011;471(7338):325–30. PMID: 21297615.
[343] Takeda A, et al. *Nature.* 2009;460(7252):225–30. PMID: 19525930.
[344] Stefater JA, et al. *Nature.* 2011;474(7352):511–5. PMID: 21623369.

Blood Diseases

Chronic anemias result from a deficiency of red blood cells or an abnormality in hemoglobin production, as is the case with sickle cell diseases 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.

NIH supports research on the causes, prevention, and treatment of nonmalignant blood diseases, including anemias, sickle cell disease, and thalassemia; premalignant processes such as myelodysplasia and myeloproliferative disorders; hemophilia and other abnormalities of hemostasis and thrombosis; and immune dysfunction. 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, sickle cell disease),
- 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, and
- Translational applications of new insights and knowledge gained from basic research in these areas towards 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 in heritable blood diseases, and the measurement and chelation of tissue iron in iron overload disorders.

A common treatment for severe anemia is blood transfusion. However, multiple transfusions can lead to iron overload which can be toxic to certain organs, in particular the liver and heart. While there are drugs to reduce iron levels, additional strategies to treat anemia and limit iron overload are needed.

When mice with β-thalassemia were genetically altered to make more hepcidin than usual, they exhibited not only reduced organ iron overload, but also a remarkable improvement of their anemia. These findings led the scientists to suggest that the development of therapeutic interventions that could increase hepcidin levels or act similarly to hepcidin might help reduce excess iron absorption in individuals with β-thalassemia.[345]

Fetal hemoglobin is replaced by adult hemoglobin within the first year after birth. Reactivation of fetal hemoglobin can treat red blood cell diseases like sickle-cell anemia. Scientists recently reported that a small deletion in a region of chromosome 6 may be the most significant functional variant accounting for different levels of fetal hemoglobin (HbF) in people of Chinese, European, or African American ancestry. A DNA fragment surrounding this deletion site was shown to regulate expression of the gene for gamma globin—a component of HbF—when tested *in vitro*. In particular, gamma-globin gene activation was found to be stronger when this short stretch of DNA was deleted than when it was present.[346]

Priority research areas identified by NIH include the Stimulating Hematology Investigation: New Endeavors (SHINE) program, which is intended to promote innovative, high quality hematology research relevant to the mission of the NIDDK. In the SHINE program, NIDDK invites investigator-initiated research project grant applications in specific areas of basic and translational hematology research where needs and opportunities for progress are particularly timely. Specific research topic areas supported by the SHINE program include: ribosomes and their role in disease; non-erythroid expression and function of erythropoietin receptors; heme regulation during erythropoiesis; anemia of inflammation and of chronic disease; iron overload; and biology and pathophysiology of myelodysplastic syndrome.

Chronic Fatigue Syndrome

Chronic fatigue syndrome, sometimes referred to as myalgic encephalomyelitis, is a complex, multi-symptom condition characterized by overwhelming fatigue that is not improved by bed rest and that may be worsened by physical or mental activity. Chronic fatigue syndrome is diagnosed 2–6 times more often in women than men. Chronic fatigue syndrome is difficult to diagnose because of multiple diagnostic criteria used by various practitioners. Exacerbating the difficulty of diagnosis is a lengthy timeframe for occurrence and recurrence of the symptoms. For example, the definition used by the CDC Web site on chronic fatigue syndrome indicates that in order to be diagnosed with chronic fatigue syndrome, a patient's symptoms must have persisted or recurred during six or more consecutive months of illness.

The etiology of chronic fatigue syndrome 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 chronic fatigue syndrome is made.

[345] Gardenghi S, et al. *J Clin Invest*. 2010;120:4466–77. PMID: 21099112.
[346] Farrell JJ, et al. *Blood*. 2011;117:4935–45. PMID: 21385855.

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.

NIAID is supporting a multi-site study designed to address whether a murine retrovirus (designated XMRV, xenotropic murine leukemia virus-related virus) is associated with chronic fatigue syndrome. Researchers at Columbia University are collaborating with geographically distributed clinicians to ensure enrollment of a definitive, representative sample of chronic fatigue syndrome patients across the U.S. Researchers are comparing blood and plasma samples from patients diagnosed with chronic fatigue syndrome to samples from healthy people who have not been diagnosed with chronic fatigue syndrome and who are matched to the affected patients by age, sex, and geography. Patient enrollment began in fall of 2011, and results are expected in 2012.

Several other ICs support research in this field. NCI supports both intramural and extramural research on viruses linked to both cancer and chronic fatigue syndrome, in addition to research on mechanisms underlying pain and fatigue in cancer, which may have applications to these symptoms in chronic fatigue syndrome. Chronic fatigue syndrome 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. NINDS supports extramural chronic fatigue syndrome research directed at effects on the central nervous system, including the role of brain mast cells in central nervous system inflammation, cognitive behavioral stress management to improve symptoms of chronic fatigue syndrome, and categorization of affected patients based on cerebrospinal fluid assays for the purpose of developing personalized treatments.

NIH hosted a *State of the Knowledge Workshop on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research* April 7–8, 2011, on the NIH campus in Bethesda. The conference was open to the public and was attended in person by over 100 people and viewed by over 900 virtual attendees. The workshop brought together 32 investigators from a wide variety of scientific disciplines to discuss chronic fatigue syndrome research. The workshop panelists identified gaps in knowledge and opportunities for new biomedical research on this disease. This workshop was sponsored by the ORWH in collaboration with the Trans-NIH ME/CFS Research Working Group.

The International Workshop on XMRV, co-sponsored by NIH, DHHS, and Abbott Diagnostics, was convened on September 7–8, 2011 on the NIH campus, Bethesda. Attracting an international audience of over 200 participants, the two-day event combined a series of plenary talks with updates on different aspects of XMRV research, addressing basic gammaretrovirus biology, host response, association of XMRV with chronic fatigue syndrome and prostate cancer, assay development, and epidemiology.

In May of 2011, NCI scientists, in collaboration with NCI-supported researchers from Tufts University, published a study in *Science* showing that XMRV was generated by recombination of two endogenous

mouse viruses in a human tumor xenograft during passage in nude mice.[347] This study provided strong evidence that XMRV was a laboratory contaminant, not a virus that infects humans.

The NHLBI-led Blood XMRV Scientific Research Working Group published an article in *Science* in September 2011 stating that comprehensive independent investigation, with blinded samples tested across nine laboratories, failed to detect reproducibly the presence of Xenotropic Murine Leukemia Virus (MLV)-related Virus (XMRV) or MLVs in the blood of 15 subjects previously reported to be XMRV/MLV-positive (14 with chronic fatigue syndrome) and from 15 healthy donors previously determined to be negative for the viruses.[348]

A study from the CDC showed that commercial laboratory reagents and human DNAs were contaminated with mouse DNA, which could have contributed to false positive assays for XMRV.[349] These reports, and a number of other published reports that failed to find XMRV in samples from human patients, led to the retraction of the original study linking XMRV and chronic fatigue syndrome.[350] A recent study from the NCI showed that at least three different types of contamination contributed to reports that there was XMRV in human patient samples: XMRV virus, XMRV DNA, and mouse DNA.[351] Taken together, the available studies provide strong evidence that XMRV is not a virus that infects humans.

NIH will continue to encourage research on chronic fatigue syndrome through two funding opportunity announcements (Program Announcements): Chronic Fatigue Syndrome: Pathophysiology and Treatment[352] and Chronic Fatigue Syndrome: Pathophysiology and Treatment.[353]

The Office of the Secretary of HHS has determined that an *ad hoc* HHS working group on chronic fatigue syndrome could be beneficial for developing a Department-wide strategy to address chronic fatigue syndrome. This working group will be responsible for outlining the breadth and depth of the Department's activities on chronic fatigue syndrome and the identification of opportunities for interagency collaboration. Leadership and coordination for the development of the chronic fatigue syndrome strategy will be provided by 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. 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 chronic fatigue syndrome.[354]

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[347] Paprotka T, et al. *Science*. 2011;333:97–101. PMID: 21628392.
[348] Simmons G, et al. *Science.* 2011;334(6057):814–7. PMID: 21940862.
[349] Zheng H, et al. *PLoS One.* 2011;6(12):e29050. PMID: 22205995.
[350] Alberts B, *Science.* 2011;334(6063):1636. PMID: 22194552.
[351] Kearney MF, et al. *PLoS ONE*. 2012;7(2):e30889. PMID: 22363509.
[352] For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-12-032.html.
[353] For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-12-033.html.
[354] For more information, see http://www.hhs.gov/advcomcfs/.

Cystic Fibrosis

Cystic fibrosis (CF) is an inherited, autosomal recessive disease of the secretory glands, including the glands that make mucus and sweat. It is caused by mutations in the gene for CF transmembrane conductance regulator (CFTR), which codes for an ion channel. CF mostly affects the lungs, pancreas, liver, intestines, sinuses, and sex organs. Mucus becomes thick and sticky, accumulates in the lungs, and blocks the airways, thereby rendering them susceptible to repeated bacterial infections that can severely damage the lung. Respiratory failure due to bacterial infection is the most common cause of death in people who have CF. 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, now averaging about 37 years of age, but some are living into their 40s, 50s, or older. As more and more people with CF reach adulthood, however, it has been discovered that about half will develop cystic fibrosis related diabetes (CFRD), an unusual form of diabetes that can lead to deterioration of lung function and a poorer prognosis.

Over the past two decades CF research has greatly improved 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. Current research is focused on development and characterization of animal/cell models to understand early CF disease pathogenesis; identification of genetic and environmental modifiers of CF; molecular phenotyping of CF lung disease, liver disease, and CF-related diabetes; exploration of microbiome diversity in the CF lung and GI tract, and its role in the progression of lung and digestive diseases; understanding of mechanisms regulating infection, inflammation, and remodeling and mechanisms regulating mucociliary clearance and airway surface liquid homeostasis; and development of therapeutic and preventative efforts to forestall CF disease onset and progression.

Current CF treatments are focused on relieving symptoms and improving quality of life. Direct modulation of the underlying pathophysiological mechanisms of CF is a long-term therapeutic goal.

Current CF treatments are focused on relieving symptoms and improving quality of life. Direct modulation of the underlying pathophysiological mechanisms of CF is an attractive long-term therapeutic approach. In a recent randomized, double blind, placebo-controlled, multicenter trial, a new oral drug, VX-770, was found to be safe and to confer considerable improvement in the function of the defective ion channel in people with an uncommon *CFTR* mutation. A subsequent phase III trial published in 2011 demonstrated dramatic benefit from the drug in these patients; [355] the drug was

[355] Ramsey BW, et al. *N Engl J Med*. 2011;365(18):1663–72. PMID: 22047557. Accurso FJ, et al. *N Engl J Med*. 2010;363(21):1991–2003. PMID: 21083385; Hutt DM, et al. *Nat Chem Biol*. 2010;6(1):25–33. PMID: 19966789; Okiyoneda T, et al. *Science.* 2010;329(5993):805–10. PMID: 20595578.

approved by the FDA in 2012, and is now available to patients, marketed as Kalydeco™. Ongoing efforts include taking similar approaches to identify medications that may benefit patients with the more common *CFTR-deltaF508* mutation.[356]

Recent laboratory studies using cells that have the same genetic defect found in most patients with CF showed that the drug suberoylanilide hydroxamic acid was able to reprogram the lung cell environment to correct the CF abnormalities. Further development of novel targets for small molecule "correctors" of CF may lead to restoration of the defective ion channel. Other recent research suggests that modulating the activity of the cell's protein quality control machinery may be an important strategy for helping boost activity of the channel in some patients.[357]

Unlike type 1 diabetes, the insufficient insulin production in CFRD stems not from an autoimmune attack on the pancreas, but rather from a progressive loss of pancreatic function similar to what is seen in type 2 diabetes. And while CFRD involves insulin resistance and has other metabolic and genetic similarities to type 2 diabetes, it is not associated with being overweight or obese. Indeed, a serious concern regarding CFRD is that it tends to induce weight loss in CF patients, who are often underweight already. However, it was unclear whether people with the disease were likely to face the same array of other serious complications endured by people with more common forms of diabetes. Thus, many health care providers were therefore reluctant to prescribe insulin for CFRD, because no one knew whether insulin, or indeed any drug used to treat other forms of diabetes, would help people with CFRD to be healthier. Recent research demonstrated that insulin therapy indeed can help people with CFRD maintain their body weight, improve lung function, and feel healthier.[358]

Although the genetic cause of CF has long been understood, unaccounted for was the wide range of symptoms observed in CF patients, even among those who share identical CFTR mutations. Investigators found regions on chromosomes 11 and 20 that can modify the effects of the CFTR mutations by ameliorating or exacerbating the disease as it progresses. They tested DNA from 2,464 CF patients, then replicated their findings and confirmed their results in 973 additional CF patients. Better understanding of how CFTR mutations are modified by regions of chromosomes 11 and 20 could lead to improved therapies tailored to the individual genetic profiles of CF patients.[359]

Bacterial clusters (known as biofilms) living in the lungs of CF patients are highly resistant to killing by antibiotics. A key cause of resistance is that bacteria become starved for nutrients during infection. It was previously thought that as the starved cells stop growing, the cellular functions targeted by antibiotics are no longer active, reducing the effectiveness of the drug. These findings suggest new

[356] Accurso FJ, et al. *N Engl J Med*. 2010;363:1991–2003. PMID: 21083385; Ramsey BW et al. *N Engl J Med.* 2011;365(18):1633–72. PMID: 22047557.
[357] Ramsey BW, et al. *N Engl J Med.* 2011;365(18):1633–72. PMID: 22047557.
[358] Moran A, et al. *Diabetes Care*. 2009;32(10):1783–8. PMID: 19592632.
[359] Wright FA, et al. *Nat Genet*. 2011;43(6):539–46. PMID: 21602797.

approaches to improve treatment for a wide range of infections and restore antibiotic efficacy to available drugs.[360]

The mechanistic link between missing CFTR and hyperabsorption of sodium in airway epithelia in CF has remained elusive, but recent findings indicate that when the epithelial sodium channel (ENaC) is associated with normal CFTR, it is protected from proteolytic cleavage and activation. In contrast, the most common form of mutant CFTR fails to protect ENaC from proteolytic cleavage and stimulation. These results indicate that CFTR down-regulates sodium absorption by limiting proteolytic cleavage of ENaC.[361]

Researchers recently produced pigs and ferrets with the same genetic mutation that causes most CF in humans. Pigs represent an attractive model for the study of CF lung disease, because their lungs share many anatomic, biochemical, and physiologic features with the human lung. During their first six months of life, CF pigs spontaneously developed lung disease, including the hallmark features of infection, inflammation, remodeling, and mucus accumulation. Importantly, the CF pigs were found to have a defect in their ability to eliminate bacteria from the airways, and this was evident within hours of birth and preceded any inflammatory reaction. Hence, infection may represent an initial step in the disease process that initiates the cascade of inflammation and pathology in CF lungs. The recently developed ferret model of CF manifests the multi-organ system involvement characteristics of human CF disease (including spontaneous development of diabetes) and provides another valuable model for dissecting early CF disease pathogenesis, determining how systemic disease in CF patients influences the progression of early lung disease, and developing novel prevention and therapeutic strategies.[362]

New information from the CF pig model indicates that loss of CFTR-dependent anion transport (chloride and bicarbonate) in newborn pigs is in itself sufficient for CF lung disease, as there was no evidence of excessive sodium reabsorption or airway surface liquid depletion in the airways of newborn pigs. Earlier studies suggested that increased sodium reabsorption and depletion of airway surface liquid may be key initiating events in CF lung disease. The CF pig model will be invaluable for investigating the connection between defective anion transport and immune defects, for evaluating early interventions to correct CFTR dysfunction and prevent progression, and for determining whether effects on infection and mucociliary clearance are primary or secondary.[363]

Priority research areas identified by NIH include:

- Elucidating the natural history and clinical manifestations of early CF lung disease;
- Exploring mechanisms of early CF lung disease using existing and recently developed animal models (mice, pigs, and ferrets);

[360] Nguyen D, et al. *Science*. 2011;334(6058):982–6. PMID: 22096200.
[361] Gentzsch M, et al. *J Biol Chem*. 2010;285(42):32227–32. PMID: 20709758.
[362] Stoltz DA, et al. *Sci Transl Med*. 2010;2(29):29ra31. PMID: 20427821. Sun X, et al. *J Clin Invest.* 2010;120(9):3149–60. PMID: 20739752.
[363] Itani OA. *Proc Natl Acad Sci U S A.* 2011;108(25):10260–5. PMID: 21646513. Chen JH, et al. *Cell.* 2010;143(6):911–23. PMID: 21145458. Pier G, et al. *Nat Med*. 2011;17(2):166–7. PMID: 21297610.

- Exploring mechanisms for the development of CF liver disease and CF related-diabetes and understanding their impact on morbidity and mortality;
- Determining the role of mutant CFTR in airway growth and development;
- Developing an array of biomarkers (including non-invasive markers) of early CF lung disease onset and progression;
- Determining the mechanisms underlying early lung disease and of disease heterogeneity in CF;
- Exploring the role of CF modifier genes and their associated variants (identified by GWAS) in CF disease pathogenesis and disease outcome;
- Developing enabling technologies/tools/animal models of lung disease that are viable long term and allow examination of early CF lung pathogenesis onset and progression; and
- Developing novel preventive or therapeutic strategies to delay or mitigate early CF lung disease (in animal models and infants and young children).

In August 2011, NHLBI issued an initiative inviting grant applications to investigate the early origins of CF lung disease and the mechanisms involved in the development and progression of pulmonary abnormalities in infants and young children with this condition.[364] In October 2011, NIDDK issued an initiative inviting grant applications to investigate the causes and consequences of CFRD. Review of these applications is underway.[365]

Transplantation

Since the first successful kidney transplant between identical twins in 1954, transplantation has become the treatment of choice for end-stage organ failure. Despite tremendous progress, however, major barriers still remain to the overall success of transplantation. These include immunological incompatibility between donor and recipient, acute rejection, chronic graft dysfunction, and complications from requisite long-term use of immunosuppressive drugs. NIAID 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.

It has been observed that some liver transplant recipients who stop taking their immunosuppressive drugs because of other health problems have continued to have a well-functioning liver without rejection. During FY 2010 and FY 2011, NIAID sponsored a clinical study to establish the feasibility of immunosuppression withdrawal in pediatric living donor liver transplant recipients. In this study, 20 children who were transplanted with a lobe of liver donated by a parent, and who had been doing well on immunosuppressive drugs for many years, were selected for study. Over a period of 6 months, the

[364] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-12-035.html.
[365] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-11-025.html.

doses of their anti-rejections drugs were slowly reduced until finally the drugs were stopped altogether. The results will be published in FY 2012.

As a result of Highly Active Anti-Retroviral Therapy (HAART), persons 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. NIAID sponsored research on outcomes of kidney transplantation and immunosuppression in people infected with HIV. In a multi-center study, 150 people with well-controlled HIV infection underwent kidney transplants, and were treated with standard anti-rejection drugs along with HAART. The results, published in FY 2011, showed that patient survival rates at 1 year and 3 years were 95 percent and 88 percent; 90 percent of the transplanted kidneys were still functioning well one year after the transplant, and 74 percent were functioning 3 years after the transplant. A higher-than-expected rejection rate was observed: 31 percent at one year, and 41 percent at three years. HIV infection remained well controlled. This research demonstrates that people with well-controlled HIV infection can have acceptable outcomes after kidney transplantation, and that more research is needed to determine the best immunosuppressive regimen for them.[366]

"Transplantation tolerance" refers to the condition in which a person can have a healthy, well-functioning transplanted organ without needing to take immunosuppressive drugs. Eliminating the need for immunosuppressive drugs is an important goal of transplantation research; however, there is currently no simple test that would tell doctors which patients might do well if they stopped taking their drugs. NIAID-sponsored research in which investigators identified the largest reported cohort of tolerant renal transplant recipients, as defined by stable graft function and receiving no immunosuppression for more than 1 year, and compared their gene expression profiles and peripheral blood lymphocyte subsets with those of subjects with stable graft function who are receiving immunosuppressive drugs, as well as with healthy controls. The results, published in FY 2010, showed that Tolerance of a transplanted kidney was strongly associated with a B cell signature using several blood and urine tests. Tolerant subjects showed increased expression of multiple genes that control B cell development. A set of just 3 of these genes distinguished tolerant from nontolerant recipients. These results point to a critical role for B cells in regulating the body's response to a transplanted kidney and might prove useful in determining which transplant recipients could do well with less or no anti-rejection medication.[367]

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 Research Consortium studies how the HLA region, a highly variable region of an individual's DNA, is associated with many immune-mediated diseases, including transplantation rejection and graft failure. The Nonhuman Primate Islet/Kidney Transplantation Tolerance program evaluates the safety and efficacy of existing and new techniques that can help transplant recipients tolerate transplanted tissues and have improved long-term

[366] Stock PG, et al. *N Engl J Med.* 2010;363(21):2004–14. PMID: 21083386.
[367] Newell KA, et al. *J Clin Invest.* 2010;120(6):1836–47. PMID: 20501946.

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, studying 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.

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 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, women are affected with MS at almost twice the rate of men.

NIH recognizes that more needs to be done to close the gaps in knowledge and reduce the rising impact of autoimmune diseases. NIH is committed to advancing the understanding of how autoimmune diseases develop and to applying results of basic research to improve the health and quality of life of patients affected with these diseases.

The most common of these diseases include systemic lupus erythematosus (SLE), MS, type 1 diabetes, autoimmune thyroid diseases, myasthenia gravis, scleroderma, inflammatory bowel diseases (IBD) 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 central nervous system in MS. In contrast, nonorgan-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 burden of these diseases is immense and includes 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 (ADCC), 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 Disease Research

NIH funding for autoimmune diseases research was $856 million in FY 2010, and $869 million in FY 2011 for non-ARRA (regular appropriations) and $125 million in FY 2010 for ARRA appropriations.[368]

Summary of NIH Activities

Collectively, NIH-funded research seeks to understand the onset and progression of over 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.

NIAID-supported research on autoimmune diseases focuses on the immunologic basis of disease, including the fundamental immunologic principles underlying disease onset and progression, developing 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 (co-sponsored by ORWH) conduct collaborative research including clinical trials of immunomodulatory therapies and mechanistic studies, and enable partnerships among clinicians and basic researchers. 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, rheumatoid arthritis, MS, ulcerative colitis, scleroderma, pemphigus vulgaris, and type 1 diabetes. Two clinical trials were recently completed for treatment of pemphigus with infliximab and for treatment of Sjögren's with Rituximab. The Centers have also published several articles that provide more detailed understanding of the tublointestinal inflammation in human lupus, and human regulatory T cells (Tregs) in healthy subjects and those with type 1 diabetes, findings that one day may lead to better treatments.

The NIAID Immune Tolerance Network (ITN) 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 ITN study showed that treatment with intravenous rituximab and steroids for patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis produced the same outcome as the treatment that has been used for more than 40 years. However, the new treatment regimen requires a much shorter treatment duration and early results suggest that the regimen elicits better response in patients with disease relapses.

The Cooperative Study Group for Autoimmune Disease Prevention (CSGADP) conducts research on the development of new therapeutic targets and approaches to prevent autoimmune diseases (co-sponsors:

[368] For funding of various Research, Condition, and Disease Categories (RCDC), see http://report.nih.gov/categorical_spending.aspx.

NIDDK and JDRF). In 2010, CSGADP supported 21 pilot projects that may lead to the development of novel targets for disease prevention or assays for biological markers of disease progression. CSGADP will be renewed in fiscal year 2012.

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-sponsor: 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 intramural research program (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 also are 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 auto-reactive cells that are capable of causing autoimmune disease. These studies are elucidating the different types of Treg cells and providing clues to how they may be used most effectively for immunotherapy of autoimmune diseases.

- Research to determine how dysregulation of the early events in B-cell receptor signaling may contribute to autoimmunity. B cells are driven to proliferate, differentiate, and produce antibodies, including autoantibodies, by signals provided through these receptors.

- Research to apply their fundamental discovery that antigens, the substances that trigger an immune response, will induce the programmed death of activated T cells that cause autoimmunity. NIAID scientists are testing in mice a new treatment for autoimmune conditions that will specifically kill the cells that are responsible for the disease. Efforts are principally directed at type I diabetes, MS, and autoantibody-mediated diseases, but the approaches involve fundamental mechanisms of the immune system and may be applicable to many, if not all, autoimmune diseases.

- Investigation of the immune responses at mucosal surfaces of the respiratory, gastrointestinal, and urogenital tracts and the diseases that can result from these responses. These studies have led to new insights into the causes of Crohn’s disease and ulcerative colitis, as well as the development of treatments for these illnesses.

- Studies of the autoimmune lymphoproliferative syndrome (ALPS), 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. ALPS can cause anemia (low red blood cell count), thrombocytopenia (low platelets), and neutropenia (low neutrophil count).

NIDDK funds a wide range of research on type 1 diabetes, inflammatory bowel diseases, celiac disease, and other autoimmune diseases. For example, Type 1 Diabetes TrialNet is an international network of researchers who are exploring ways to prevent, delay, and reverse the progression of type 1 diabetes. TrialNet screens large numbers of individuals and conducts trials of agents to prevent type 1 diabetes in at-risk people and to slow progression of the disease in people who are newly diagnosed. The Environmental Determinants of Diabetes in Youth (TEDDY) study has completed enrollment of over 8,000 high-risk newborns and is collecting biosamples for analysis to identify potential triggers of type 1 diabetes. Identification of an infectious agent that triggers autoimmunity could lead to a vaccine to protect against type 1 diabetes. Or, if dietary factors are identified that protect from or contribute to development of the disease, changes to infant feeding practices could be recommended.

The NIDDK Inflammatory Bowel Disease (IBD) Genetics Consortium 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 genome-wide association studies of adult and pediatric populations over the past several years to uncover several genetic variants associated with ulcerative colitis and Crohn's disease.

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 is part of the Molecular Physiology and Therapeutics Branch in NIDCR. The mission of the Clinic is to develop new therapies based on better understanding of the pathogenesis of this disease. The Clinic designs studies to address unmet clinical needs, bridge traditional medical specialties, and fosters close collaboration between clinical and basic scientists.

The International Sjögren's Syndrome Registry is funded by NIDCR, NEI, and ORWH. The goal of the registry is to promote research on Sjögren's syndrome, with an emphasis on diagnosis, epidemiology, causes, prevention, and treatment.

A number of research efforts are underway examining the potential role of a number of different microRNAs in Sjögren's syndrome. A microRNA is a very short piece of RNA found in the cells of plants, animals, and humans. MicroRNAs are key orchestrators of genome functions in both normal development and in disease. Investigators are examining how microRNA expression affects salivary flow, as well as using microRNA expression profiles as biomarkers of salivary gland inflammation in Sjögren's syndrome. Two microRNAs have been validated as markers of inflammation and researchers are in the process of creating a standardized assay for examination of those markers in a larger clinical cohort. Additionally, a large-scale effort is underway to determine the global expression of microRNAs and other non-coding short RNAs present in salivary secretions and salivary glands in Sjögren's syndrome patients and healthy volunteers. The research data are expected to be of considerable use in allowing the development of diagnostic and disease progression biomarkers that can reflect the physiological status of the salivary gland without the need of a biopsy and invasive procedures.

NIDCR's current active clinical protocols include:

- Screening Protocol for Salivary Gland Dysfunction: The goal of this study is to evaluate patients with complaints of dry mouth to determine the cause and severity of their salivary gland dysfunction and their possible eligibility for other NIDCR protocols.

- Pathogenesis of Sjögren's Syndrome: The purpose of this study is to 1) collect long-term clinical and laboratory data to identify pathogenetic mechanisms and the natural history of Sjögren's syndrome by careful clinical evaluation of participants over time; 2) collect information on symptoms as identified through general medical, oral, and eye examinations and laboratory assessments; 3) collect blood samples for current and future laboratory studies related to the pathogenesis of Sjögren's syndrome; and 4) identify participants eligible for other Sjögren's syndrome protocols.

- Parotid irrigation: The purpose of the study is to determine whether irrigation of the parotid gland with low-dose topical dexamethasone improves parotid salivary gland flow in Sjögren's syndrome subjects. Participants will have up to seven outpatient visits over 56 days. Parotid glands will be treated with dexamethasone and saline (salt water) to evaluate if the dexamethasone helps to increase saliva production.

Because autoimmune disorders disproportionately affect girls and women, ORWH has had a lengthy record of research support for these conditions, and has partnered across the NIH ICs.

Some of the FY 2011 grants focus on specific autoimmune disorders such as MS, RA, or SLE. ORWH has also contributed continuously to the Autoimmune Centers of Excellence, which support clinical trials and basic research on new immune-based therapies for a variety of autoimmune disorders. In FY 2011, ORWH supported several innovative areas of study, such as predictors of pregnancy outcome in SLE and antiphospholipid syndrome, and the study of a new molecular pathway which is likely to be important in the pathogenesis and treatment of MS.

In FY 2010, investigators made a major clinical advance in treating people with a severe form of vasculitis known as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, a rare but devastating disease of blood vessels. In FY 2011, based on the results of an ITN Phase II/III clinical trial, the FDA approved rituximab in combination with glucocorticoids to treat patients with Wegener's granulomatosis and microscopic polyangiitis, two rare forms of autoimmune disorders that affect small blood vessels in kidney, lung, sinuses, and a variety of other organs. This is the first FDA-approved treatment for these rare and relapsing diseases.[369]

Several research groups have demonstrated that induced specialized immune cells known as inducible regulatory T cells have less stability in vivo than natural regulatory T cells and that inducible regulatory T cells may actually develop into effector T cells that can cause autoimmune disease. Effector T cells are responsible for most of the cellular immune responses against invading pathogens and certain

[369] Stone JH, et al. *N Engl J Med*. 2010;363(3):221–32. PMID: 20647199.

malignancies. NIAID scientists have conducted pre-clinical studies that emphasize the need for characterizing inducible regulatory T cells, as these cells interact with immune molecules and can affect proteins involved in immune system response. By understanding more about inducible regulatory T cells, scientists may one day be able to manipulate these cells to treat human autoimmune disease.[370]

Researchers, including those in NIDDK's IBD Genetics Consortium, identified 30 new genetic regions associated with Crohn's disease, doubling the number of associated genetic variants.[371] In a separate study, 29 new genetic variants that increase the risk for ulcerative colitis were identified. Based on these analyses, the total number of identified IBD risk loci has increased to 99, with 28 genetic variants in common between ulcerative colitis and Crohn's disease.[372] Finding new genetic variants will help scientists discover the molecular pathways that contribute to these diseases and can lead to new therapeutic targets.

In NIDDK-sponsored research on a mouse model of celiac disease, when the mice were fed gliadin, a component of the dietary protein gluten, the inappropriate intestinal immune reaction that is mounted against the gliadin was further promoted by feeding retinoic acid, a form of vitamin A, to the animals. Therefore, in this context, retinoic acid further enhances inappropriate immune responses, rather than protecting against them as it does in other immunological settings. This study yielded a new animal model of early-stage celiac disease to enable future research, and warns against using vitamin A or retinoic acid as a treatment for patients with celiac disease.[373]

Pathogenic T helper cells are an important factor in many autoimmune diseases. For example, stimulation of the receptor for the signaling lipid sphingosine-1-phosphate (S1P1) simultaneously produces proinflammatory and anti-inflammatory effects. S1P1 acts through the enzyme mTOR, which is targeted by two immunosuppressive drugs—rapamycin, which is used to prevent transplant rejections, and FTY720, a promising oral therapy for MS. These drugs have been shown to regulate the balance between inflammatory T helper 1 and suppressive T regulatory cells, and provide new insights into autoimmune disease pathogenesis, and potential therapeutic strategies.[374]

Recent research indicates that three proinflammatory cytokines—interleukin-6 (IL-6), IL-1ß, and IL 23—are sufficient to induce T helper 17 cell differentiation in a mouse model. Inducing T helper 17 cell differentiation can cause severe autoimmune disease, as the cells are involved in inflammation and tissue damage. The research shows that transforming growth factor ß—previously thought to be essential—is not critical to T helper 17 cell formation. These findings provide new insights into the factors in autoimmunity, and possibilities for targeted therapies.[375]

Interferon regulatory factor 5 (IRF5) regulates the activity of type 1 interferons and other proinflammatory cytokines during viral infections and in some autoimmune diseases, and

[370] Chen Q, et al. *J Immunol*. 2011;186(11):6329–37. PMID: 21525380.
[371] For more information, see http://www.nature.com/ng/journal/v42/n12/full/ng.717.html.
[372] For more information, see http://www.nature.com/ng/journal/v43/n3/full/ng.764.html.
[373] For more information, see http://www.nature.com/nature/journal/v471/n7337/full/nature09849.html.
[374] For more information, see http://www.nature.com/ni/journal/v11/n11/full/ni.1939.html.
[375] For more information, see http://www.nature.com/nature/journal/v467/n7318/full/nature09447.html.

polymorphisms in the IRF5 gene have been associated with several autoimmune rheumatic diseases. In a model of inflammation, histone deacetylases and histone acetytransferases alter the IRF5 protein, causing increased inflammation. Thus, IRF5 regulates inflammation in conjunction with histone deacetylases and histone acetyltransferases. Understanding how IRF5, histone deacetylases, and histone acetyltransferases mediate inflammation could inform therapeutic strategies for treating autoimmune diseases.[376]

A comprehensive map of specific and unique microRNA "signatures" from a variety of lymphocytes provides new understanding of epigenetic regulation of microRNA expression during lymphocyte development, differentiation, and in the immune response. MicroRNAs are key orchestrators of how the genome functions. These insights into mechanisms of how immune cells regulate internal conditions to maintain health and function and the immune response will support further investigations in immune dysfunction and autoimmunity.

Uveitis is a collection of acute and chronic vision-threatening conditions with various causes, but all resulting in inflammation in the eye. In 2010, the NEI-funded Standardization of Uveitis Nomenclature Working Group achieved consensus on clinical grading of ocular inflammation and standardization of research reporting, which facilitated meta-analyses across standardized clinical studies and provides a common language to describe inflammatory conditions. In autoimmune diseases, the T cells, which normally function to attack microbes start to attack the body's own cells, often by releasing chemical messages called interleukins. Regulatory T cells combat these autoreactive T cells waging chemical warfare by releasing protective interleukins. One recently identified type of helper T cell (Th17) has emerged as a key factor in the pathogenesis of ocular inflammation. A robust experimental model of autoimmune uveitis helped resolve the complex roles of Th17 cells, interleukin 21, and other helper and regulatory T cells. Autoimmune uveitis is currently treated with corticosteroids and sometimes systemic immunosuppression, although this research shows that blocking specific interleukins may be sufficient in the future. In 2011, the first large randomized clinical trial comparing current uveitis treatments provided important information on treatment outcomes of different regimens.

For the mouse embryonic salivary gland, NIDCR investigators recently demonstrated[377] that stimulation by the cholinergic parasympathetic nerves is required for maintenance of rare cells that circulate in the blood with the ability to differentiate into cells that make up the lining of blood vessels. Their finding may signal new ways to regenerate salivary glands in patients who have lost salivary gland function, and suggests that nerve-dependent organ regeneration is relevant to the growth and regeneration of other organ systems.

Identified genes regulating the formation of the branched epithelial structures were found in multiple organ systems including lungs, mammary, and salivary glands, indicating that temporary loss of cell-cell interactions enables formation and propagation of clefts within sheets of cells[378]. These researchers were able to show that in mice, these genes were involved in both mammalian salivary gland and lung

[376] For more information, see http://www.jimmunol.org/content/185/10/6003.long.
[377] Knox SM, et al. *Science*. 2010;329:1645–7. PMID: 20929848.
[378] Onodera T, et al. *Science*. 2010;329:562–5. PMID: 20671187.

branching morphogenesis, suggesting this conserved process could be important in efforts to regenerate functional salivary glands and other branched organs.

NIDCD-funded scientists recently explained how glucocorticoids, a commonly prescribed family of drugs to treat hearing loss related to autoimmune diseases such as lupus and rheumatoid arthritis, do not work on inflammation as previously thought, but appear to correct an imbalance in ions in the fluid of the inner ear. The research team hypothesizes that developing a treatment based on regulating ion concentration, instead of controlling inflammation, may be more effective and offer fewer side effects than steroids for people with autoimmune-related hearing loss.[379]

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 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 systemic lupus erythematosus or rheumatoid arthritis. 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 the immunosuppressive drug methotrexate to treat rheumatoid arthritis and cancer, doctors have been substituting methotrexate for long-term treatment with glucocorticoids. NIDCD supported a large clinical study to determine whether methotrexate is effective in treating ASNHL. Unfortunately, the study showed that methotrexate was not effective in maintaining hearing recovery in individuals with ASNHL who had been previously treated with high-dose glucocorticoids. NIDCD now intends to fund research projects to better understand the mechanisms of ASNHL and develop new diagnostic tests. NIDCD hopes that this investment will translate into less toxic diagnostics and therapies that preserve natural hearing.

The Cooperative Study Group for Autoimmune Disease Prevention (CSGADP), a collaborative network of investigators who focus on halting the development of autoimmune diseases at early disease stage by means other than global immunosuppression, were renewed in FY 2012. In 2010, CSGADP supported 21 pilot projects to test approaches that may lead to the development of novel targets for disease prevention or assays for biological markers of disease progression. CSGADP is cofounded by NIDDK and the Juvenile Diabetes Research Foundation International.

In 2010, NIAID established the Human Immunology Project Consortium (HIPC) program as part of the overall NIAID focus on human immunology. Through the HIPC, centralized research resources and a comprehensive, centralized database will be constructed for use by the greater scientific community. The information gained will provide a comprehensive understanding of the human immune system and its regulation and will also serve as a foundation for the future study of immune-mediated diseases in

[379] Trune DR, Kempton, JB. *J Neuroimmunol*. 2010;229(1–2):140–5. PMID: 20800906.

the human, such as allergy, asthma, transplant rejection, and autoimmune diseases, and a variety of inflammatory diseases.

NIDDK plans to continue its vigorous support of research related to autoimmune diseases within its mission. For example, the over 8,000 participants being followed in TEDDY provide an unparalleled resource to study the development of the human microbiome from birth through childhood. Planned studies will build on research in mice to identify how interaction between the immune system and bacteria in the gut may alter the risk of T1D. (Other future research directions related to type 1 diabetes are found in the “Chronic Diseases and Organ Systems” section of this chapter.)

With NIDDK support, the Methotrexate Response in Treatment of Ulcerative Colitis (MERIT-UC) trial will be launched to investigate the therapeutic value of methotrexate (MTX) in adult UC patients for whom established therapies have failed.

NIDCR-supported scientists are working to validate salivary diagnostic biomarkers and to develop the related testing apparatus for Sjögren's syndrome. Sjögren’s Syndrome is also the focus of a genome-wide study to identify genetic factors that contribute to the disorder. Gene therapy is being evaluated for its potential for inserting molecules such as cytokines that could modulate inflammation in salivary glands to slow or prevent their destruction in Sjögren’s syndrome. Also, the capacity to produce molecules that enhance saliva production by residual salivary gland cells might be introduced by gene transfer. Eventually, development of artificial salivary glands may have application in patients who have lost all functional salivary glands because of radiation treatment or Sjögren’s syndrome.

Infectious Diseases and Biodefense

NIH builds and maintains a base of fundamental knowledge about infectious and immune-related diseases and uses that knowledge to develop new and improved diagnostics, therapeutics, and preventive measures, including vaccines. At the same time, NIH continues to develop a flexible domestic and international infrastructure that allows it to respond to newly emerging and re-emerging threats wherever they occur, thereby protecting public health in the U.S. and abroad.

Infectious diseases are caused by microbial pathogens—bacteria, viruses, fungi, protozoa, and helminths (worms)—that invade the body and multiply, causing physiological damage and illness. Pathogens 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, and some forms of viral hepatitis are transmitted through exposure to blood or other body fluids; and malaria is caused by a microscopic parasite that is transmitted by an insect "vector," in this case a mosquito. Transmissible infectious diseases can devastate large human populations rapidly and easily cross international borders.

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, biological toxins, chemical weapons such as nerve gas, or radioactive substances.

The NIH biodefense strategy integrates basic, applied, and clinical research knowledge and capabilities into a flexible and adaptable approach designed to create interventions that target single as well as multiple pathogens. 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.

Although NIAID has primary responsibility for infectious diseases and biodefense research, many other NIH ICs play critical roles, including FIC, NEI, NICHD, NIDDK, NIEHS, NIGMS, NINDS, and OAR. All of the NIH ICs support AIDS-related research activities, consistent with their individual missions. The ICs that conduct most of the research on AIDS and its associated co-infections, malignancies, cardiovascular and metabolic complications, and behavioral and social science issues are NIAID, NIDA, NCI, NIMH, NCRR, NICHD, NIDDK, and NHLBI. All NIH AIDS research is coordinated by OAR.

NIH-wide research on 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. Translational research builds on basic research findings with the aim of developing new and improved diagnostics, therapeutics, and vaccines. NIH conducts and supports clinical research to assess the efficacy and safety of candidate drugs, vaccines, and other products. As NIH pursues these goals, an overarching priority is to reduce health disparities and improve health for all people.

Infectious diseases and biodefense inherently are global concerns. Among U.S. academic institutions and scientists there is rapidly growing interest in the expansion of 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. It 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, many of which share an interest in the scientific opportunities provided by global research.

NIH supports and conducts research on hundreds of pathogens and the diseases they cause, including HIV/AIDS, TB, malaria, and emerging and re-emerging infectious diseases, such as hemorrhagic fevers caused by Ebola and other viruses, West Nile virus, Lyme disease, prion diseases, plague and other diseases caused by biodefense pathogens, and influenza .

NIH research on biodefense and emerging and re-emerging infectious diseases is fully integrated and includes the development of infrastructure and capacity-building, that is, scientific and human resources needed to conduct research on pathogens safely and effectively; basic research on microbes and host immune defenses; the targeted development of medical countermeasures, including vaccines, therapeutics, and diagnostics; and training for emergency and skilled workers that would be needed in the event of a biological, chemical, or radiological weapons attack or other public health emergency.

Infectious diseases cause approximately 26 percent of all deaths worldwide. Each year, more than 11 million people die from infectious diseases; the vast majority of deaths occur in low- and middle-income countries. The infectious diseases that today cause the greatest number of human deaths worldwide are lower respiratory infections, HIV/AIDS, diarrheal diseases, malaria, and TB.[380] The top infectious disease killers in those countries for people ages 15 to 59 are HIV/AIDS, TB, and lower respiratory infections.[381] Worldwide, HIV causes nearly 2.0 million deaths each year,[382] TB kills 1.4 million each year,[383] and lower respiratory infections in 2008 caused an estimated 3.46 million deaths.[384] Malaria is a serious problem, especially in Africa, where one in every five childhood deaths is due to the effects of the disease.[385]

Each year infectious diseases kill approximately 6.5 million children, most of whom live in developing countries. For children younger than age 14, infectious diseases account for seven of the top 10 causes

[380] For more information, see http://www.dcp2.org/main/Home.html.
[381] For more information, see WHO *Disease Control Priorities Project* Infectious Diseases chapter (April 2006) http://www.dcp2.org/file/6/DCPP-InfectiousDiseases.pdf.
[382] For more information on the global HIV/AIDS pandemic, see http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2009/2009epidemic_update.asp.
[383] For more information on tuberculosis, see http://www3.niaid.nih.gov/topics/tuberculosis.
[384] For more information, see http://www.who.int/mediacentre/factsheets/fs310/en/index.html.
[385] For more information, see http://www.who.int/features/factfiles/malaria/en/index.html.

of death. In this age group, the leading infectious diseases are lower respiratory infections, diarrheal diseases, and malaria.[386]

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 one in five deaths in that region. Africa and the most populous countries of Asia harbor the largest number of TB cases. Together, Bangladesh, China, India, Indonesia, and Pakistan account for half of new TB cases each year.

In the United States, infectious diseases add significantly to the overall burden of illness. Together, influenza and pneumonia account for more than 50,000 deaths annually.[387] More than 1.2 million people are living with HIV in the United States, and each year brings another 50,000 new infections. Unfortunately, approximately one-fifth of those people living with HIV are unaware of their infection.[388] An estimated 2.7 to 3.9 million people in the U.S. have chronic hepatitis C, and 800,000 to 1.4 million are affected by chronic hepatitis B.[389]

Many infectious diseases increasingly are difficult to treat because pathogens are developing resistance to antimicrobial drugs.[390] For example, in recent years there have been dramatic increases in antiretroviral drug resistance in HIV, chloroquine resistance in malaria, the emergence of multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB), and methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

NIH Funding for Infectious Diseases and Biodefense Research

NIH funding for infectious diseases research was $3,890 million in FY 2010 and $3,883 million in FY 2011 for non-ARRA (regular appropriations) and $568 million in FY 2010 for ARRA appropriations.[391] NIH funding for biodefense research was $1,794 million in FY 2010 and $1,803 million in FY 2011 for non-ARRA (regular appropriations) and $221 million in FY 2010 for ARRA appropriations.[392]

Summary of NIH Activities

NIAID conducts and supports basic research to better understand infectious agents and the response of host organisms by studying the cellular and molecular biology of pathogen and host, physiologic

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[386] For more information, see WHO Disease Control Priorities Project, Infectious Diseases chapter (April 2006) http://www.dcp2.org/file/6/DCPP-InfectiousDiseases.pdf.
[387] For more information, see FASTSTATS - Deaths and Mortality http://www.cdc.gov/nchs/fastats/deaths.htm.
[388] For more information on the latest U.S. HIV/AIDS statistics from CDC, see http://www.cdc.gov/hiv/topics/surveillance/index.htm.
[389] For more information, see http://www.cdc.gov/hepatitis/PDFs/disease_burden.pdf.
[390] For more information about antimicrobial resistance, see http://www.niaid.nih.gov/topics/antimicrobialresistance/Pages/default.aspx.
[391] For funding of various Research, Condition, and Disease Categories (RCDC), see http://report.nih.gov/categorical_spending.aspx.
[392] 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.

processes, and genome sequences and structures. Their findings elucidate pathogen entry mechanisms, survival strategies, and immune evasion techniques; evolutionary adaptations; activation of the host immune system; and cellular and whole organism responses to infection and vaccination. The following describe selected NIAID basic research activities; NIAID also supports a broad portfolio of investigator-initiated basic research.

NIAID supports 11 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs). The overall goal of the RCEs 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 countermeasures against biodefense and emerging infectious disease agents. To date, over 2000 papers have been published by RCE-supported scientists.

NIAID is tackling some of the most vexing questions in the study of human immunology through its Human Immunology Project Consortium. Launched in 2010, the Consortium supports research to define functionally relevant changes in the human immune system, through human (rather than animal) studies, in response to vaccination or infection. The Consortium was funded in its first year by the American Recovery and Reinvestment Act, and contributes to developing technologies to accelerate discovery. Findings will assist in development of vaccines and other interventions for a variety of infectious diseases including influenza, malaria, tuberculosis, and HIV/AIDS.

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.

Two NIAID initiatives are energizing the adjuvant research field. NIAID established the *Innate Immune Receptors and Adjuvant Discovery Program* in FY 2003/2004 and renewed it in FY 2009. Currently, investigators supported by this program are working to identify and characterize novel compounds to be used as vaccine adjuvants to prevent infection or as stand-alone immunotherapeutics for the treatment of acute infection. To move beyond discovery, NIAID initiated the *Adjuvant Development Program* in FY 2008. This program supports preclinical studies of lead vaccine adjuvants to bring them toward licensing for human use.

The *NIAID Strategic Plan for Research on Vaccine Adjuvants*, released in 2011, describes NIAID's future plans for adjuvant research. The plan originated from a blue ribbon panel of experts convened by NIAID in November 2010. With existing productive programs and clear steps to achieve the plan's ambitious goals, continued NIAID investment will contribute to the success of future adjuvants and development of improved protective vaccines, and may reduce illness-associated healthcare costs.

How immunity develops at the earliest stages of life, such as within the first year after birth, remains a mystery. Unlike adults, infants lack the ability to mount strong, protective, targeted antibody and cellular immune responses to infectious diseases. Infants can receive antibodies from their mothers while breastfeeding, but cellular immunity cannot be passively transferred. Understanding how the

infant immune system develops could provide insights into improving the effectiveness of vaccinations against common childhood infections.

In FY 2011, NIAID announced a new initiative, the *Infant Immune System: Implications for Vaccines and Response to Infections* program. This program supports research to understand how the innate and adaptive immune responses mature and to determine how the immune system learns how to tolerate non-pathogenic bacteria that reside in the intestinal tract.

Infectious organisms are a major cause of pregnancy complications, including premature labor and maternal and fetal death and disease. Problems with the placenta are a major cause of fetal death, and studies have suggested that undiagnosed infection of the placenta and/or the fetus may be a significant cause of unexplained stillbirths. However, the mechanisms of placental and fetal infection and disease development are poorly understood. In FY 2011, NIAID partnered with NICHD to solicit proposals for new and innovative studies of infectious organisms (pathogens) that affect placental function and fetal well-being. The knowledge gained through this initiative will provide a basis for developing interventions against these pathogens, and for meeting the long-term goal of reducing their adverse impact on pregnancy and fetal health.

Major Infectious Diseases

NIH conducts research on hundreds of infectious diseases, with special emphasis on those that claim large numbers of lives each year. 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, the elderly, adolescents, young children, and infants. NIH also explores how human behaviors as well as social, cultural, economic, and geographic factors affect disease transmission. The ultimate goal is to translate knowledge gained through basic research into interventions that improve public health in the U.S. and other countries.

HIV/AIDS

HIV/AIDS remains a leading cause of death worldwide, especially in sub-Saharan Africa. Although not as prevalent in the United States, 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 illnesses remain a significant cause of morbidity and premature mortality. Without an effective preventive vaccine or improved treatments that allow HIV-infected individuals to discontinue ART, the burden of HIV/AIDS will increase as new infections and use of ART continue to rise. The NIH is committed to developing new prevention methods and treatment strategies in the hopes of achieving an “AIDS-Free Generation” through the combined use of prevention and treatment tools.

The best long-term hope for controlling the AIDS pandemic 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. This is one of the highest research priorities of the NIH. In October 2010, the New England Journal of Medicine published the results of the AIDS vaccine trial RV144. Better known as the “Thai

Trial," RV144 was the first HIV vaccine trial to demonstrate a modest reduction in the risk of HIV transmission (31.2 percent efficacy) and thereby provide the long sought after proof-of-concept that it is possible to induce an immune response against HIV in humans with a vaccine. The vaccination approach utilized a novel prime-boost vaccine strategy that involves two components: the "prime" with a replication-defective pox virus that included genetic components of HIV, and the "boost" with a recombinant HIV envelope protein. NIH will build on the results of the RV144 vaccine trial through the Pox-Protein-Public-Private-Partnership (P5) initiative. The P5 will advance a similar HIV vaccination strategy through clinical development and, if successful, to licensure, based on testing in populations with high HIV incidence in Southern Africa and Thailand.

New vaccine concepts spawned through basic research and developed through translational studies are critical for providing novel vaccine strategies. In 2010, NIH-led scientists discovered and characterized human antibodies that can block a wide range of HIV strains from infecting human cells in the laboratory. Understanding how these antibodies neutralize HIV could serve as the foundation for the rational design for future vaccine candidates. In addition, a new AIDS vaccine research consortium is supporting basic and translational research to better understand the earliest events of mucosal HIV infection and how vaccines can be optimized to block these early events by inducing protective mucosal immune responses.

NIH continues to investigate treatment as a strategy to prevent new HIV infections--a promising new area of HIV/AIDS prevention research. An NIH clinical trial utilizing supported pre-exposure prophylaxis (PrEP) as a prevention method demonstrated that male-to-male transmission of HIV was reduced in high risk individuals who were treated with daily antiretroviral drugs. Furthermore, the NIH conducted a phase III clinical trial which showed that in HIV-discordant, heterosexual couples, HIV transmission to uninfected partners was reduced by 96 percent if antiretroviral treatment was started earlier in the HIV-infected partners. This unprecedented result from the study known as HPTN052 was selected as the 2011 "Breakthrough of the Year" by the journal *Science*. Indeed, research shows that HIV treatment can prevent HIV transmission, 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. Therefore, a priority research area for NIH is to create the infrastructure and linkages needed to implement the "Seek, Test, Treat, and Retain" strategy, which *seek*s out high-risk, hard-to-reach vulnerable populations (e.g. substance abusers), *tests* them for HIV, *begins treatment* in those who test positive, and *retains* patients in treatment and monitors their care. NIH is launching additional clinical trials to evaluate further how testing, treatment, education/counseling, and awareness can prevent HIV at both the community and population levels.

Another key strategy in HIV prevention is the use of ART to prevent mother-to-child transmission (MTCT). In 2010, based on the results of two NIH-funded studies, the World Health Organization revised its guidelines for the use of ART in both mothers and infants to minimize the development of drug-resistant HIV during treatment for MTCT. The NIH also initiated the PROMISE (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 babies during pregnancy and breastfeeding while preserving the health of these children and mothers.

NIH is also committed to improving the outcomes of HIV treatment by developing strategies to minimize morbidity and mortality associated with ART. For example, the *Strategic Timing of Antiretroviral Therapy (START)* study will determine the optimal time to initiate treatment of asymptomatic HIV-infected individuals to maximize their long-term health.

The ultimate improvement in HIV treatment would be the development of novel therapeutics or treatment regimens that would result in complete eradication of residual HIV or long-term HIV remission so that ART is no longer necessary for HIV-infected individuals. NIH supported two new funding opportunities for research that aims to achieve these outcomes. The program *Basic Research in HIV Persistence,* which began in 2010, seeks to increase understanding of the mechanisms that lead to HIV persistence and to identify the location of persistent reservoirs in individuals on ART. Similarly, the *Martin Delaney Collaboratory* supports basic and translational research in HIV persistence and latency with the end goal of identifying novel therapeutics and strategies to target and eliminate HIV reservoirs in HIV-infected individuals.

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.

NIH is supporting research to develop better, less toxic treatments and to investigate how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors interact to affect treatment success or failure and/or disease progression. Studies will continue to address the increased incidence of malignancies, neurologic, 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 tropical parasitic disease in terms of annual mortality. About 3.3 billion people—half of the world's population—are at risk of contracting malaria. Worldwide, an estimated 216 million clinical cases of malaria occurred in 2010.

People living in the poorest countries are the most vulnerable to malaria. Malaria is an especially serious problem in Africa, where one in every five childhood deaths is attributed to the disease. An African child has on average between 1.6 and 5.4 episodes of malaria fever each year. Every 50 seconds, a child dies from malaria. The magnitude of worldwide disease burden and the existing barriers to controlling infection, disease, and transmission require multiple approaches for 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.

In FY 2010, NIAID announced approximately $14 million in first-year funding to establish 10 new malaria research centers in regions where malaria is endemic, including parts of Africa, Asia, the Pacific Islands, and Latin America. The International Centers of Excellence for Malaria Research (ICEMR) program will generate knowledge, tools, and evidence-based strategies to control malaria. Specifically, the ICEMRs are studying the complex interactions between the human host, the malaria parasite, the vector, and the ecology at the molecular, cellular, organism, population, and field levels. The ICEMRs also work with local governments, agencies, and academic institutions to enhance and sustain local laboratory and clinical research capacity.

NIAID-supported investigators also are working to develop a vaccine against malaria. NIAID currently provides product development support for eight malaria vaccine candidates in clinical trials. An effective malaria vaccine would produce large economic benefits by reducing healthcare costs and helping to stabilize the economies of countries where malaria is endemic. Initial positive results reported last year by the PATH Malaria Vaccine Initiative, GlaxoSmithKline Biologicals and their collaborators came as welcome news. In a late-stage clinical trial in approximately 6,000 African children, the candidate vaccine, known as RTS,S, reduced malaria infections by roughly half.[393] Studies testing another malaria vaccine candidate in humans have started at the NIH Clinical Center, with results expected in 2012.

As part of its commitment to the Global Health Initiative, NIAID partners with organizations such as USAID, WHO, the Commission of the European Community, the European-Developing Countries Clinical Trials Partnership (EDCTP), the European Vaccine Initiative (EVI), the Wellcome Trust, the Bill & Melinda Gates Foundation, the PATH Malaria Vaccine Initiative (MVI), the Medicines for Malaria Venture (MMV), and the Multilateral Initiative on Malaria (MIM). Additionally, NIAID supports the Global Malaria Action Plan (GMAP),[394] an international framework for coordinated action designed to control, eliminate and eradicate malaria and 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.

[393] For more information, see http://www.ncbi.nlm.nih.gov/pubmed/22007715.
[394] For more information, see http://www.rbm.who.int/gmap/gmap.pdf.

In 2011, researchers identified bacteria that render mosquitoes resistant to malaria parasites. Further study is needed,[395] but it may one day be possible to break the cycle of infection by reducing the mosquito's ability to transmit malaria parasites to people.

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, NITD609, was identified by an international team of NIAID-funded extramural and intramural investigators following an analysis of over 12,000 chemicals using a robotic screening technique customized to detect compounds active against the most deadly malaria parasite. A clinical trial to assess NITD609's activity in people has begun in Thailand. Research on NITD609 is a continuing collaboration among NIH-funded scientists, the pharmaceutical company Novartis, and the nonprofit Medicines for Malaria Venture.

Tuberculosis

Tuberculosis (TB) remains a major cause of disability and death worldwide. Each year, more than 9 million people around the world become sick with TB and nearly 1.4 million people die of TB-related causes. The recent emergence of drug-resistant TB poses a major global health threat. NIAID has a long-standing effort to understand how TB causes disease, and is expanding its TB research agenda and capabilities to meet the challenge of drug resistance.

The World Health Organization estimates that almost half of all people with drug-resistant TB in 2008 were in China and India, with each reporting approximately 100,000 new cases. In response to this growing international public health challenge, NIAID has expanded its TB research in these areas. For example, NIAID and Chinese officials with the Henan Provincial Health Bureau launched the first study of the Sino-U.S. (Henan) Tuberculosis Prevention and Treatment Research Institute in Zhengzhou, China. The Institute will develop diagnostic tools, treatment options, and prevention methods for multidrug-resistant and extensively drug-resistant TB. NIAID is also contributing to the establishment of research cohorts in India in order to identify biological markers of infection and disease for TB, in the presence and absence of co-infections and co-morbidities that contribute to the TB epidemic in this country.

Among people with HIV/AIDS, TB is a major co-infection and the leading cause of death, responsible for killing approximately 350,000 HIV-infected individuals in 2010. The HIV/AIDS Networks plan to expand their capabilities so that they can address key scientific questions regarding the high rate of TB co-infection in HIV-infected individuals. 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 to assure that opportunities for contributing to the development of new health care interventions are realized. Through its Genomics Centers and Bioinformatics Resource Centers/Databases, NIAID is initiating collaborations with research partners in TB endemic countries. These studies are designed to provide insight into the genetic diversity of *Mycobacterium tuberculosis* and catalog genetic markers that underlie resistance to first and

[395] For more information, see http://www.niaid.nih.gov/news/newsreleases/2011/Pages/MalariaBacteria0513.aspx.

second line drugs. Genomics data and analysis from these studies will be made publicly available through NCBI 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. NIAID's product development infrastructure, through its preclinical and clinical services programs, has contributed to the advancement of many drugs, vaccines and diagnostics that are part of the global TB product pipeline. Preclinical and clinical studies on new TB drugs and vaccines are benefitting from 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 *M. tuberculosis*.

NIAID's strategic efforts in coordination benefit all aspects of NIAID's TB Program, from developing biomarkers and rapid, sensitive diagnostics to stimulating the development of preventive measures such as vaccines and treatments for latent (dormant) TB infections; to accelerating the development of new treatments by running adaptive Phase II combination trials, in which trial arms are added or dropped based on the interim trial results.

Some recent activities in TB research include the following:

- Researchers are studying the epidemiology of drug resistant and drug sensitive Mtb strains in communities to determine their genetic makeup and assess whether genetic diversity impacts transmission and development of disease.

- The biochemistry and life cycle of Mtb can provide critical information needed to identify points of vulnerability against which novel drugs can be directed. Some projects are studying the bacteria as a whole and understanding the coordination of multiple pathways to ensure that these drugs are relevant within the context of a living organism.

- The NIAID-funded Cambodian Early Versus Late Introduction of Antiretroviral Drugs (CAMELIA) clinical trial showed that the survival of untreated HIV-infected adults who were newly diagnosed with TB could be prolonged by starting antiretroviral therapy two weeks after beginning TB treatment, rather than waiting the standard eight weeks.

- Researchers are studying the ability of selected small molecule chemicals to interfere with Mtb viability and growth for the purpose of developing drug candidates with novel mechanisms of action that can be used against drug sensitive and drug resistant bacteria alike.

- A Phase I clinical trial is currently ongoing in healthy subjects to investigate interactions between the experimental drug TMC 207and rifabutin/rifampin with which the new drug may be combined when used to treat TB patients.

- Current methods for diagnosing TB and drug-resistant disease can take weeks, which leaves patients untreated and facilitates the spread of TB infection. To address this problem, NIAID supported the pre-clinical development of the Cepheid GeneXpert® MTB/RIF assay, which is a

fully automated, simple to use diagnostic testing platform. This two-hour test detects *Mycobacterium tuberculosis*, the bacterium that causes TB, and also detects resistance to rifampin, an antibiotic commonly used to treat TB. The World Health Organization recently endorsed, the Cepheid Xpert MTB/RIF® assay, for further evaluation and use in global diagnosis of drug-resistant TB. The cost of the test has just been significantly reduced to make use in resource constrained settings more affordable.

- Investigators found that an experimental vaccine composed of a genetically modified bacterium closely related to the bacterium that causes TB protects mice against TB infection. The research was funded in part by NIAID.

- NIAID-funded researchers are developing a number of other novel vaccine candidates, several of which have entered human clinical trials. These vaccines are designed to accomplish several different goals: preventing infection, halting progression to active disease; and contributing to the effectiveness of drugs by mobilizing the host immune response.

Viral Hepatitis

At least five different hepatitis viruses (A through E) cause liver disease in humans. All five can cause acute hepatitis, while hepatitis B, C, and D viruses can also lead to a persistent infection and chronic hepatitis. (Additional information on viral hepatitis is included in the Chronic Diseases and Organ Systems section under "Digestive Diseases.") Collectively, viral hepatitis is the most common cause of acute and chronic liver disease in the U.S. and worldwide. Chronic hepatitis B affects an estimated 800,000 to 1.4 million people in the U.S., and chronic hepatitis C affects an estimated 2.7 to 3.9 million people in the U.S.[396] 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.

NIDDK supports several research programs related to viral hepatitis, including The Hepatitis B Research Network, established in 2008 to advance understanding of disease processes and natural history of chronic hepatitis B, as well as to develop effective approaches to treatment with currently available therapies. The Network brings together clinical centers from throughout the U.S. and Canada. This multi-center Network is enrolling patients in multiple clinical trials in both adults and children with hepatitis B. In addition to the Network, NIDDK funds follow-up and ancillary studies of completed clinical trials on hepatitis C, including the Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C (Peds-C) trial; Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial; Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C); and Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL), which is investigating approaches to mitigate recurrent hepatitis C infection after liver transplantation.

NIAID research is advancing or has helped to advance the development of new therapeutic agents for HCV (e.g., HCV Entry Inhibitor ITX 5061 [A5277], HCV Protease Inhibitor Boceprevir [A5294]) and adjunct treatments (e.g., pioglitazone, nitazoxanide) to increase response rate to pegylated interferon plus

[396] For more information, see http://www.cdc.gov/hepatitis/PDFs/disease_burden.pdf.

ribavirin treatment for HIV/HCV co-infected patients (A5239, A5269). 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.

In FY 2010, NIAID renewed support of the Hepatitis C Cooperative Research Centers, a network of five centers dedicated to defining successful immune response to HCV infection and to identifying new targets for antiviral drugs, vaccines, and other therapeutic strategies for the prevention or treatment of acute and chronic HCV infection. Research conducted at the Centers will continue to advance understanding of the immune response to infection and the factors that determine the outcome of infection, either spontaneous or therapy-induced clearance or chronic persistence of HCV.

NIAID intramural researchers, whose work has resulted in a marketed vaccine for hepatitis A and an effective hepatitis E vaccine, collaborate with partners worldwide to study the basic immunology of HCV infection in chimpanzees and humans and prospects for vaccine development. While current intramural research studies use chimpanzees, NIAID will phase out this research over time. Note: The recent IOM committee on the use of chimpanzees in biomedical and behavioral research did not reach a consensus decision on whether chimpanzees are essential to the development of a prophylactic HCV vaccine and if or how much the use of chimpanzees would accelerate or improve this work.

In FY 2011, NIAID funded three collaborative partnerships for research on HBV through the Partnerships for Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens initiative. These partnership awards will help advance the development of new classes of therapeutic drugs for HBV.

Researchers in the NIDDK's Peds-C Study Group conducted a clinical trial that showed combination therapy with the antiviral drugs peginterferon and ribavirin is more effective than therapy with peginterferon and placebo in treating chronic hepatitis C in children.[397]

In an NIDDK-supported study, scientists found that a dietary supplement, S-adenosylmethionine (SAMe), safely and effectively boosts response to combination antiviral therapy for hepatitis C in adults infected with a form of the virus that typically does not respond as well to such therapy.[398]

NIAID-funded researchers found that liver cell death is increased in the presence of HCV and HIV compared to HCV or HIV alone. These results provide an additional mechanism for the accelerated liver disease progression observed in HCV–HIV co-infection.[399]

Two cell membrane proteins, CD81 and occludin, are the minimal human factors required to render mouse cells permissive to HCV entry *in vitro*. Researchers funded by NIAID demonstrated the expression

[397] Schwarz KB, et al. *Gastroenterology*. 2011;140(2):450–8. PMID: 21036173.
[398] Feld JJ, et al. *Gastroenterology.* 2011;140(3):830–9. PMID: 20854821.
[399] Jang JY, et al. *J Hepatol*. 2011;54(4):612–20. PMID: 21146890.

of these proteins allows HCV infection in fully immunocompetent inbred mice. This is an important breakthrough towards a small animal model that can be used in HCV vaccine research.[400]

NIAID-sponsored scientists showed the membrane-bound transcription factor CREB3L1 is activated in response to virus infection and inhibits proliferation of virus-infected cells. Because HCV infection often progresses to persistence, these results imply that CREB3L1 has to be silenced to enable HCV replication, providing a new line of investigation into the mechanism of chronic HCV persistence.[401]

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: understand the infectious agent and how it causes disease, and develop tools to diagnose, treat, and prevent illness caused by that microbe.

NIAID's research efforts have evolved over the past decade from developing vaccines for specific pathogens to focusing on the fundamental basic research needed to better understand infectious agents. The goal of this basic research is to lay the groundwork for developing broad-spectrum antibiotics and antivirals—drugs that can prevent or treat diseases caused by multiple types of bacteria or viruses—and multi-platform technologies that potentially could be used to more efficiently develop vaccines against a variety of infectious agents.

This move from the "one bug-one drug" approach toward a more flexible, broad approach using sophisticated genomic and proteomic technologies has yielded numerous scientific advances and has equipped the United States with a much more integrated, coordinated approach to addressing public health crises. This was demonstrated during the SARS epidemic, pandemic flu preparedness efforts resulting from the H5N1 avian influenza outbreak, and the 2009 H1N1 influenza pandemic.

In addition to supporting and conducting basic, translational, and clinical research to develop safe and effective medical countermeasures, NIH supports programs to expand research infrastructure. NIH also provides a broad array of preclinical and clinical research resources and services to researchers to bridge gaps in the product development pipeline and lower the financial risks incurred by industry in the development of novel antimicrobials.

[400] Dorner M, et al. *Nature*. 2011;474:208–11. PMID: 21654804.
[401] Denard B, et al. *Cell Host Microbe*. 2011;10(1):65–74. PMID: 21767813.

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; a vaccine against smallpox and another against 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 smallpox, anthrax, Ebola, Marburg, botulism, and pandemic influenza, many of which pose potential threats to the United States and international communities. As noted previously, central to this research is NIAID's effort to change the paradigm for antimicrobial drug development from a "one-bug, one-drug" approach to a focus on broad-spectrum therapies that could be used against entire classes of pathogens. NIAID recently awarded four 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: A recent study showed that an experimental Ebola vaccine developed by NIH researchers protects monkeys against not only the two most lethal Ebola virus species for which it was originally designed but also against a newer Ebola virus species that was identified in 2007.

- Prions: NIH researchers developed a method that is 10,000 times more sensitive than other methods to detect variant Creutzfeldt-Jacob disease (vCJD) in blood plasma. vCJD is a type of prion disease, diseases caused by infectious proteins, in humans that leads to brain damage and death. NIH researchers also used the test to rapidly detect scrapie, a prion disease of sheep.

- Hendra: A series of studies including some supported and conducted by NIH led to the development of a human monoclonal antibody that can protect monkeys from Hendra virus disease. Hendra virus infection of humans is rare but the fatality rate is 60 percent or more. In May 2010, shortly after the NIH study in monkeys successfully concluded, Australian health officials requested the antibody for emergency use in a woman and her 12-year-old daughter who were exposed to Hendra virus. Both the woman and child survived and showed no side effects from the treatment.

- Chikungunya: An experimental vaccine to prevent chikungunya fever, a viral disease spread by certain species of mosquitoes, is being tested in a clinical trial conducted by NIH scientists. The vaccine was developed by researchers at the NIAID Vaccine Research Center (VRC). Chikungunya fever is an emerging global health concern. Although it is generally not fatal it can cause debilitating symptoms, most often fever, headache, and severe joint pain that can last from a few weeks to several months. If successful, the approach used to develop the vaccine may be

used to create vaccines against other viruses transmitted by mosquitos such as Western, Equine, and Venezuelan equine encephalitis.

- Broad-spectrum Therapeutics: A team of scientists led by an NIAID researcher developed a novel treatment capable of protecting mice against the bacteria that causes tularemia, a highly infectious disease of rodents that is sometimes transmitted to people and is also known as rabbit fever. In additional experiments with human immune cells, the treatment also demonstrated protection against bacteria that cause plague, melioidosis, and brucellosis.

- NIAID-supported researchers identified a small-molecule broad-spectrum antiviral, named LJ001, with significant activity against multiple deadly viruses, including HIV-1, Ebola, Rift Valley Fever, influenza, and Nipah virus. Researchers identified LJ001 after screening about 30,000 molecules to find one capable of blocking the entry of the deadly Nipah virus into a host cell. Subsequent testing found that the compound also blocked other lipid-enveloped viruses, suggesting that it likely targets a component common to all of the viruses.

- Anthrax: At the start of infection, anthrax bacteria (*Bacillus anthracis*) release a toxin that binds to immune cells through two receptors, TEM8 and CMG2, found on the cell surface. NIH researchers conducted experiments in genetically modified mice that lack the CMG2 receptor. The researchers concluded that B. *anthracis* uses CMG2 receptors to impair the scavenging action of neutrophils and macrophages during early infection, giving the bacteria time to multiply to levels sufficient to overwhelm the body's defenses. Developing drugs and vaccines that block *B. anthracis* from establishing early infection via binding to CMG2 may be crucial for treating and preventing anthrax disease. Although the FDA-licensed BioThrax vaccine is proven to be effective and safe against all forms of anthrax infection, it requires an initial five doses and yearly boosters. An improved vaccine formulation AV7909 induces significantly improved immune response with only two doses. To support further development of this much improved anthrax vaccine, NIAID supported the GMP manufacturing, NHP immunogenicity study, GLP safety and toxicity evaluation, and the development of a guinea pig post-exposure prophylaxis (PEP) aerosol challenge model. The data enabled the ongoing phase 1b trial to optimize dose/schedule for the AV7909.

- Botulism: NIAID has supported the development of XOMA 3AB, a monoclonal antibody designed to treat ingested and aerosolized botulinum toxin A, from basic research through discovery and preclinical testing. In 2011, this therapeutic entered a Phase I clinical study at a NIAID-supported clinical unit at Johns Hopkins University. NIAID also has supported the development of monoclonal antibodies against botulinum toxin types B and E with significant progress made toward identifying suitable candidates.

- Pneumonic Plague: In collaboration with the FDA, NIAID is supporting animal studies to determine whether newer antibiotics approved for other uses are also effective against

pneumonic plague. This approach may set a precedent for FDA approval of other medical countermeasures under the Animal Rule.[402]

Another priority in emerging infectious diseases includes seasonal and pandemic influenza. Each annual influenza outbreak in the United States typically occurs between December and March. Every year in the United States, on average 5 percent to 20 percent of the population contracts influenza and more than 200,000 people are hospitalized with complications from influenza infection. And each year, seasonal influenza is estimated to kill an average of 36,000 Americans.

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, it is critical to maintain a pipeline of new and improved anti-influenza medications. 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 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 rapidly mobilized 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.

The NIAID intramural research program conducts collaborative influenza research with many public and private sector partners, and in FY 2010, NIAID intramural investigators engaged in a government-wide effort to understand the pathogenesis of mild to severe pandemic influenza and facilitate the development of novel therapies and strategies for treating severe influenza. Other major research programs include: needle-free pandemic influenza vaccine development through a collaboration with MedImmune, Inc.; nasal spray vaccine development and testing against H9N2, H5N1, H7N3, H2N2 and H6N1 viruses with pandemic potential; 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 Clinical Center and elsewhere to characterize and treat severe influenza in various populations using existing and experimental therapeutic strategies.

[402] For more information, see http://www.fda.gov/downloads/EmergencyPreparedness/MedicalCountermeasures/UCM283166.pdf.

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 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. More recently, this approach was evaluated in two small clinical trials, with participants producing evidence of cross-protective antibodies. 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 are also working on novel approaches to develop a vaccine which 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.

NIAID investigators initiated collaborations with Mexican health authorities to address the impact and epidemiology of the 2009 pandemic H1N1 influenza in that country. In addition, during the course of the 2009 H1N1 influenza outbreak, NIAID conducted 12 clinical trials through its longstanding Vaccine Treatment and Evaluation Units **(**VTEUs), six of which provided information that helped build the foundation for the nationwide 2009 H1N1 immunization campaign. Trial data offered key scientific evidence essential for public health decision-making, including optimal dosage and number of doses for individuals in different age brackets and for specific high-risk groups of particular concern such as pregnant women. Studies on concurrent administration of H1N1 vaccine and seasonal influenza vaccine demonstrated that two influenza vaccines could be safely administered at the same time. NIAID-sponsored clinical trials also provided data on the use of the vaccine in selected populations with underlying health conditions, including HIV and asthma, and also examined the use of an adjuvant with H1N1 vaccine, which showed that the adjuvant was safe and could be used to stretch the vaccine supply. The information and experience that was gained from all of these clinical trials will apply well beyond the 2009 H1N1 influenza.

NIAID continues to support the Centers for Excellence in Influenza Research and Surveillance (CEIRS) Program. The CEIRS Program is an integrated network of five centers that was established in 2007, building upon an NIAID-funded program begun at St. Jude’s Children’s Hospital in 1999. The Program brings together multidisciplinary teams of researchers to expand the NIAID influenza virus surveillance program, both internationally and in the United States, 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 causes 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.

NIAID supported the development of the FilmArray Respiratory System, which is capable of simultaneously detecting 15 respiratory viruses (including several influenza strains) in one hour. The initial FilmArray system was approved by the FDA in 2011. Since 2005, NIAID has awarded small business grants and NIAID partnerships to Idaho Technology, Inc., to support development of this multiplex

diagnostic platform from initial prototype through the current version. This support was essential for Idaho Technology to develop the FilmArray Respiratory Panel. NIAID's preclinical resources also played a role in developing the HT-FilmArray. Influenza sequences generated by NIAID's Genomics Sequencing Centers and made available through the Influenza Research Database facilitated design of the influenza detection assays included in this platform. Avian influenza strains obtained from the BEI repository were used to validate the assays.

NIAID also supports international collaborations, including through the Southeast Asia Infectious Diseases Clinical Research Network, which has assembled a 17-site network in Thailand, Vietnam, and Indonesia to address issues of emerging influenza viruses and other emerging infections, as well as in Mexico, where five sites in Mexico City address the impact and epidemiology of influenza-like illness in the region.

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.

The NIAID-sponsored *Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance* program[403] explores improved treatment strategies to help reduce the risk of antimicrobial resistance and preserve the effectiveness of existing drugs. NIAID now supports eight large-scale clinical trials 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 methicillin-resistant *Staphylococcus aureus* (CA-MRSA).

The *Partnerships for the Development of Therapeutics and Diagnostics for Drug-Resistant Bacteria and Eukaryotic Parasites* initiative focuses on advancing the development of diagnostics and therapeutics for drug-resistant pathogens. Nineteen projects were awarded in 2010. In addition, NIAID issued the *Partnerships for Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens*[404] funding announcement in FY 2010 to address the threat to public health presented by drug resistance in the *Clostridium difficile* bacteria, which causes severe intestinal disease, in *Neisseria gonorrhoeae*, which causes gonorrhea, and in strains of hepatitis B virus.

In FY 2011, NIAID issued 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 2011 aims to discover and develop therapeutics that target host functions required for infection, replication, spread and/or pathogenesis by priority

[403] For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-AI-10-020.html.
[404] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-10-010.html.

pathogens. Research supported in this program suggests that an intervention that targets the essential host function would have broad-spectrum efficacy. Moreover, targeting a host function reduces selective pressure on the microbe to acquire resistant mutations, making resistance less likely to emerge. When using the knowledge gained to develop drugs targeted against host functions with that known about microbial pathogenesis, significant steps could be made leading to the treatment of many microbial threats, including priority pathogens deemed highly threatening to public health.

Dengue fever, a mosquito-borne flu-like illness that can turn deadly, continues to increase in the tropics and subtropics. It has the potential to spread in temperate zones and appears to be increasing in severity. NIAID dengue research priorities include elucidating the viral/human genetics and immunological factors that contribute to disease severity and the pre-clinical development and clinical evaluation of rapid diagnostics, therapies, and vaccines against dengue. The dengue research program received an important boost from American Recovery and Reinvestment Act, which NIAID used to advance studies of the immune responses to viral infection and the effects of mucosal dengue vaccination and other novel vaccine development strategies. In 2010, NIAID researchers announced they had developed an experimental vaccine against dengue after ten years of research. Clinical trials to evaluate the safety of this vaccine in healthy adults are underway in the United States and trials are planned in dengue-endemic countries. Other NIAID-supported investigators are developing vaccines using a variety of technologies to improve the delivery methods and ability to stimulate an immune response to dengue infection. For example, NIAID recently awarded a contract to develop a novel dengue vaccine that can be delivered through the skin without the use of needles and to evaluate this vaccine for safety and immunogenicity in clinical trials in the United States and abroad. Two other vaccines, whose development was partially supported by NIAID, are currently being tested by companies. Altogether, the Institute supports a wide array of dengue research activities and will continue to do so until the disease is under control or eliminated.

NIH also 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 the NIH and the U.S. Department of Defense, 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 CounterACT Research Network solicited proposals from academia, other governmental agencies, and industry. In Fiscal Year 2006, the CounterACT Research Network established four Research Centers of Excellence in Medical Chemical Research. The network enabled the development of therapeutics for cyanide, nerve agents, chlorine, sulfur mustard, and radiation exposures. Training of personnel remains a critical facet of 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 (SEIU) to provide high-quality training for hazardous materials emergency responders.

NIH continues to lead HHS efforts to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage. Many candidate medical

countermeasures are in the early stages of discovery, including medical countermeasures for hematopoietic acute radiation syndrome (ARS), gastrointestinal ARS, radiation-induced lung pneumonitis and/or fibrosis, and other radiation-induced injuries. Key efforts underway focus on developing decorporation agents-- specific drugs that remove radioactive isotopes from the body. Three orally bioavailable decorporation agents moving toward Investigational New Drug Application submission will be used to treat victims with internal radionuclide contamination from fallout or "dirty bombs". At the same time, an IND for an oral decorporation agent has been filed with the FDA and the project is now being funded by HHS/BARDA for advanced development.

NIAID established the Centers for Countermeasures Against Radiation (CMCR) program in 2005 in an effort to develop medical products to diagnose, prevent and treat the short- and long-term consequences of radiation exposure after a radiological or nuclear accident or terrorist attack. The program supported over 100 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 United States. The program has yielded include numerous publications, and several patents were filed. The efforts of CMCR helped to revitalize an area of science that had been dormant for many years. To expand on these efforts, NIAID agreed to provide five years of additional funding to the program beginning in fiscal year 2010. Seven academic institutions from across the country participated in the renewed program. A progress report detailing the research priorities for the nuclear/radiation countermeasures program was published in 2012.[405]

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. The physical and intellectual research infrastructure that NIAID has built over the years 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:

- *National and Regional Biocontainment Laboratories* are 14 extramural laboratories that provide BSL-4/3/2 and BSL-3/2 biocontainment facilities, respectively, for research on biodefense and emerging infectious disease agents. The biosafety labs also are available or under construction, and prepared to assist national, state, and local public health efforts in the event of a bioterrorism or infectious disease emergency. In addition to their own research, the labs support the NIAID Biodefense Research Agenda.

- *Cooperative Centers for Translationa*l *Research on Human Immunology and Biodefense* consists of eight centers that aim to translate research on immunity to infection into clinical applications to protect the public against bioterrorist threats.

- *Vaccine and Treatment Evaluation Units (VTEUs)* are clinical sites located at universities nationwide that provide extensive clinical trials capacity and expertise. The VTEUs played a key role in testing the vaccine for the 2009 H1N1 influenza pandemic.

[405] For more information, see http://www.niaid.nih.gov/topics/radnuc/Documents/radnucprogressreport.pdf.

- *The HIV/AIDS Clinical Trials Networks* is an ongoing robust research program in HIV/AIDS currently being expanded to add capacity to address AIDS co-morbidities such as tuberculosis and hepatitis. In addition, NIAID unveiled plans to create a new clinical trial network focused on antibacterial resistance.

- *NIAID genomics activities*. NIAID has developed a comprehensive genomics program. In addition to sequencing thousands of microbial genomes, NIAID genomics activities provide the scientific community with genomic data as well as resources such as reagents, databases, software, and computational tools essential for analyzing and applying research findings. Coupled with other biochemical and microbiological information, sequence data are helping scientists to identify specific strains of microbes, develop sequence-based detection technologies and diagnostics, and identify targets for new drugs and vaccines.

- *Preclinical services*. 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 resources provided to researchers include: in vitro assessment for antimicrobial activity, animal models of infectious diseases, and therapeutic development services. Plans are underway to provide vaccine development services as well.

    - 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 conducts three types of services: development and refinement of animal models; i*n 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, including, those derived from biotechnology processes.

Controlling infectious diseases not only saves lives but 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 the U.S. President's Emergency Plan for AIDS Relief; the Global Fund to Fight AIDS, Tuberculosis, and Malaria; 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 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, tuberculosis, malaria, dengue, and neglected tropical diseases remain

endemic. The following are selected examples of NIAID's 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. The NIAID Division of Intramural Research, through long-term collaborations with colleagues in country, 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.

NIAID HIV/AIDS Clinical Trials Networks (comprising leadership groups and 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. NIAID is expanding the scope of the network's current activities to include the treatment and prevention of tuberculosis and hepatitis, major co-infections with HIV, and has also leveraged this infrastructure for an intramural study testing a new HPIV3 vaccine in infants.

South East Asia Infectious Diseases Clinical Research Network (SEAICRN) 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. In concert with the World Health Organization, the Wellcome Trust, and the ministries of the respective countries, the SEAICRN is a 17-site network in Thailand, Vietnam, and Indonesia addressing issues of emerging influenza viruses and other emerging infections. A second five-year contract for NIAID support and collaboration is currently being negotiated. 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* (La RED) 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. The five sites in Mexico City include two pediatric sites. Three studies are currently enrolling participants. Future short-term strategic goals include expansion to 1–2 sites outside of Mexico City and the start of an additional flu study. The long-term strategic plan is to promote sustainability and capacity of La Red.

Phidisa is an HIV/AIDS research collaboration with HHS through the NIAID, the U.S. Department of Defense, and the South African Medical Health Services (SAMHS). Launched in 2003, this six-site clinical research project focuses on the management and treatment of HIV infection in the uniformed members

of the South African National Defense Force (SANDF) and their dependents, with over 6,000 enrolled patients. Phidisa's mission is to generate evidence through clinical research to inform policy and improve medical care to benefit members of the SANDF and their families. Phidisa has recently expressed an interest in building capacity within the SAMHS to conduct research on other diseases of critical importance to military force preparedness.

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 VAP is co-managed by the Indian Department of Biotechnology and the NIAID and 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 VAP include malaria, TB, dengue, immune enhancement, hepatitis C, rabies, the genetics of respiratory syncytial virus, and vaccine development for rotavirus and HIV. While the VAP will continue to promote translational research and support individual projects proposed by Indian and U.S. collaborating scientists, it will also expand into new scientific areas, such as understanding human immunology and the development of novel vaccine-related technologies.

Minority Health and Health Disparities

Scientific and technological discoveries throughout the 20th century have improved the overall health of the nation 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, cardiovascular disease, diabetes, HIV/AIDS, infant mortality, and certain other conditions. These disparities in health are most visible in racial/ethnic minority groups, individuals from socioeconomically disadvantaged backgrounds, and people living in medically underserved areas, including some 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 (i.e., biological, behavioral, environmental, and 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/or 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/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 U.S. Research findings consistently have shown that many health disparity populations also are less likely than most of the majority population to receive needed health care services, including clinically necessary procedures. Health disparities frequently are associated with differences in socioeconomic status (SES) and tend to diminish significantly and, in a few cases, disappear when SES factors are controlled. Nevertheless, some racial/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 Black and Minority Health Report in 1985, 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 non-federal 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 last 25 years.

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 has not only initiated research projects with significant minority participation to compare health status between various populations, but also has given high priority to programs that focus exclusively on minority health issues. NHLBI epidemiology programs, for example, include several major studies of heart disease in minority populations, support for components of the NHANES that track prevalence and risk factors of cardiovascular and lung diseases by race and ethnicity, and the National Longitudinal Mortality Study that analyzes socioeconomic, demographic, occupational, and racial differentials in U.S. mortality. Genetic epidemiologic research includes studies of the genetics of hypertension in populations of West Africa 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 have consistently 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. In the area of lung diseases, considerable effort has been directed toward understanding the disproportionate burden of asthma among urban black and Hispanic children and identifying culturally appropriate strategies to help them achieve good symptom control. The NHLBI research program in blood diseases has, since 1972, supported an extensive array of studies to understand the pathophysiology of sickle cell disease, identify better approaches to its diagnosis and treatment, and prevent complications.

Research on aging continues to document the existence of persistent health differentials among older racial and ethnic groups in the United States, both before and after age 65. NIA remains committed to addressing health disparities and inequities with initiatives supported in partnership with the NIMHD as well as with other Institutes and Centers. 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 (RCMAR) program, the mission of which includes establishing a research mentoring mechanism in minority health and health disparities, enhancing professional diversity in minority health research, evaluating/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.[406] 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 African Americans and whites in Baltimore. This study began in 2004 and is ongoing.[407]

Many diseases and disorders within the NIDDK 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, related to type 2 diabetes, the HEALTHY[408] study

[406] For more information, see http://www.rcmar.ucla.edu/index.php.
[407] For more information, see http://handls.nih.gov.
[408] Middle-School Based Primary Prevention Trial of Type 2 Diabetes (HEALTHY). For more information, see http://clinicaltrials.gov/show/NCT00458029.

tested a middle school-based intervention for reducing risk factors for type 2 diabetes in youth; the TODAY[409] clinical trial is testing different treatment strategies in youth diagnosed with type 2 diabetes; and the Diabetes Prevention Program Outcomes Study 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 disproportionately burdened by type 2 diabetes. Additionally, the NIDDK supports the Type 2 Diabetes Genes Consortium to identify type 2 diabetes risk genes in minority populations.

Toward the goal of building and sustaining a biomedical, behavioral, clinical, and social science research pipeline focused on NIDDK mission areas, the NIDDK supports the Short-Term Education Program for Underrepresented Persons (STEP-UP). STEP-UP provides research education grants to institutions to coordinate high school and undergraduate programs that provide eligible students with 10-12 weeks of summer research experience and training opportunities. STEP-UP seeks to increase the participation of students from backgrounds underrepresented in biomedical research, including individuals from disadvantaged backgrounds, individuals from underrepresented racial and ethnic groups, and individuals with disabilities. Additionally, the NIDDK has established a Network of Minority Research Investigators (NMRI) to increase the number of minority researchers and to increase research on health disparities. The goal of the NMRI is to foster a communication network of current and potential biomedical research investigators and technical personnel from traditionally under-served communities. This Network is led by the NIDDK's Office of Minority Health Research Coordination, and currently has approximately 200 members.

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. It found that Black and Hispanic children have a higher prevalence than white children of a range of risk factors for obesity by pre-school age, including maternal depression, early initiation of solid food consumption, and intake of sugar-sweetened beverages. The results suggest that there is a need for interventions in very early life to reduce disparities in childhood and adult obesity. The article reporting these findings was named as one of the Robert Wood Johnson Foundation's Most Influential Research Articles of 2010.

The NIDDK-led Look AHEAD clinical trial is determining whether a lifestyle intervention designed to promote weight loss can improve health outcomes, including prevention of heart disease, in overweight or obese people with type 2 diabetes. For the first 4 years of the study, participants in the lifestyle intervention group lost significantly more weight and better maintained their lost weight than those in the control group; they also had improved fitness, glucose control, blood pressure, and HDL cholesterol with less use of medication. The trial is planned to continue for up to 13.5 years, and longer-term results will determine whether these effects will lead to reduced rates of cardiovascular disease and death.

[409] Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY). For more information, see http://clinicaltrials.gov/show/NCT00081328.

NIDDK-supported researchers have found that African Americans with two copies of certain variants in the APOL1 gene are at increased risk of developing kidney disease, particularly focal segmental glomerulosclerosis (FSGS) and kidney disease related to infection with the HIV. These findings explain nearly all of the excess risk of non-diabetic kidney failure in African Americans, and have important implications for understanding the differences in kidney disease risk across populations. NIMHD is collaborating with NIDDK regarding future research directions in FSGS and the APOL1 gene.

The NIMHD Centers of Excellence (COE) program has created a research platform to advance scientific knowledge and develop interventions that address diseases affecting health disparity populations. They also provide a focal point for establishing partnerships with other institutions or federal agencies interested in health disparities research. For example, NIMHD and the Environmental Protection Agency (EPA) have launched the "Environmental Health Disparities Initiative," which examines the complex relationship between health disparities and the natural, built, social, and policy environments. The principal objective of this collaborative research effort is to generate innovative approaches to alleviate environmentally driven health disparities and improve access to healthy environments for vulnerable populations.

In a recent study, the NIMHD COE at Arizona State University explored when it is most efficacious to expose Mexican heritage youth to drug abuse prevention programs. Implementing the Keepin' it REAL drug prevention program in middle school (but not elementary school) decreased the use of alcohol, cigarettes, marijuana, and inhalants by Mexican heritage youth.

A diabetes epidemic is facing the U.S. Virgin Islands, yet little is known regarding the cultural context relevant to self-management of the disease in this U.S. territory. COE researchers in the Virgin Islands conducted in-home interviews of the local population, supplemented by a self-administered questionnaire and hemoglobin A1c testing, to characterize self-management knowledge, attitudes, and behaviors among patients living with diabetes. Several recurrent themes emerged from this study: 1) cultural nuances shaped perspectives on self-management, 2) culturally-specific challenges were barriers to effective self-management, 3) medical homes were rarely viewed as the primary source of education and support, and 4) fear of largely motivated or stalled self-management practices. This study highlights the need for culturally-tailored measures and interventions to address the specific needs within this population.

Stroke affects certain ethnic and minority populations at a disproportionately higher rate than non-Hispanic whites. African Americans 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 is also higher in Mexican Americans compared with whites. Socioeconomic status only accounts for a portion of these disparities, suggesting that biological, cultural or geographic factors also may play a role. In certain areas of the southeastern U.S., stroke mortality is significantly higher than in the rest of the population. The "stroke belt" has a 40 percent higher rate, while the "stroke buckle" has a 20 percent higher rate. NINDS supports research aimed at better defining stroke risk, incidence and outcomes in the U.S. and among different sub-populations. Collection of population-based data helps identify and explain health disparities in stroke, and inform 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, about half of whom live in the "stroke belt" region of the southeastern US. This study has produced nearly 100 publications that have led to better understanding disparities in stroke in the US. Data generated from this study continue to help researchers pinpoint reasons that the stroke rate is higher in this region, and among African Americans, and to develop targeted strategies for intervention.

NINR supports a range of activities related to eliminating health disparities and promoting health equity in underrepresented populations, and to training new investigators underrepresented in the research community. NINR has recently sponsored research initiatives to reduce health disparities in minority and underserved children, and to promote health in racial and ethnic minority males. Recent studies have explored such topics as: risk factors for preterm labor and birth in African-American women and improving breast feeding in urban low-income mothers. In 2011, NINR released a Spanish-language version of its palliative care brochure to increase awareness of this comprehensive treatment for pain and other symptoms of serious illness in the Hispanic community.

The NCRR Research Centers in Minority Institutions Translational Research Network conducts multi-site clinical and translational research on diseases that disproportionately affect minority populations, such as cancer, diabetes, renal disease, infant mortality, HIV/AIDS, and cardiovascular diseases.[410]

ORWH supports trans-NIH efforts to promote research on health disparities and minority women's health. The objectives of the NIH strategic plan on women's health and sex differences research, Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research, encompass a broad vision of disease-specific research in women's health. The goal is to better understand the role of sex and gender differences in disease risk, vulnerability, progression, and outcomes for diverse populations throughout life.

Women from low SES backgrounds, especially from African American populations, are particularly susceptible to adverse pregnancy-related outcomes because of a high prevalence rate of obesity. The Weight Management in Obese Pregnant Underserved African American Women project, which is sponsored by ORWH, is testing a novel lifestyle intervention to help obese socioeconomically disadvantaged African American women achieve healthy weight control during and after pregnancy.

Epidemiology research funded by NEI, such as the Los Angeles Latino Eye Study, the Multi-ethnic Pediatric Eye Disease Study, and the Chinese American Eye Study, has pinpointed areas of health disparity in eye disease, especially glaucoma, which is the leading cause of irreversible blindness among Hispanic and African Americans, and diabetic eye disease. A genetics study comparing glaucoma in West African and American populations is pioneering new genetics techniques that require fewer patients for each analysis. Not only is the prevalence of glaucoma four times higher in African Americans than

[410] On December 23, 2011, President Barack Obama signed the Consolidated Appropriations Act, 2012 (P.L. 112-74). As part of this legislation, the National Center for Research Resources (NCRR) is dissolved and the National Center for Advancing Translational Sciences (NCATS) is established. Science Education Partnership Awards (SEPA) is now part of the NIH Office of the Director, Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs.

Caucasians, the risk of blindness is up to 10 times higher. 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 increased risk for glaucoma relative to Caucasians with similar intraocular pressures. The Diabetic Retinopathy Clinical Research Network conducts trials in community clinics that serve a diverse complement of patients with diabetic retinopathy.

Oral health in the U.S. has improved considerably, but not for all Americans. Chronic dental and oral conditions remain among the most common health problems that afflict disadvantaged and underserved communities. Among those with lower levels of access to dental care are the poor, members of minority groups, the elderly, the very young, and people living in sparsely populated rural areas where dentists are few.

The NIDCR Health Disparities Research Program supports a full spectrum of research studies that identify practical, sustainable approaches so that more disadvantaged Americans may experience good oral health. The Centers of Research to Reduce Oral Health Disparities are conducting several clinical trials aimed at reducing early childhood caries, improving the oral health of disadvantaged pregnant women, and increasing early detection of oral cancer. Data from the National Health and Nutrition Examination Survey (NHANES),[411] 1999–2004, indicate that the prevalence of decayed or filled teeth is more prevalent in U.S. children (ages 2–4 and 6–8) who are Mexican American or Black compared with their non-Hispanic white counterparts. Nearly 70 percent of Mexican American children aged 6–8 have or have had decay compared with nearly 50 percent of non-Hispanic white children. Disparities in the prevalence of untreated tooth decay persist into adulthood, with the prevalence of tooth decay being nearly twice as great for racial/ethnic minorities compared to non-Hispanic whites.

The NIEHS Partnerships for Environmental Public Health (PEPH) program focuses on research into the risk of increased health burden in populations with inequities in environmental exposure and disease.

NIMHD and NIBIB created a joint program, the Development and Translation of Medical Technologies that Reduce Health Disparities Initiative, which supports the development and translation of medical technologies aimed at reducing disparities in healthcare access and health outcomes. 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; non-invasive technologies for diagnosis and treatment; and an integrated, automated system to assess or monitor a specific condition.

NIMH has launched an administrative supplement program to support advanced research experiences for outstanding early career physicians and medical students from diverse backgrounds. As outlined in the 2008 National Advisory Mental Health Council Workgroup on Research Training,[412]

[411] Center for Disease Control and Prevention, *National Health and Nutrition Examination Survey*, Atlanta, Georgia, 1999–2004. Available at http://www.cdc.gov/nchs/nhanes.htm.
[412] For more information, see http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/investing-in-the-future.pdf.

NIMH encourages the recruitment, training, and retention of outstanding physician-scientists from diverse backgrounds. 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.

NIH outreach initiatives encompass a wide range of endeavors, including communications and education programs, partnerships and collaborations with public and private organizations, and enhancement and expansion of access to information and services among disadvantaged populations. Outreach initiatives span many forms of activity, from creation of a new slogan to promote early stroke awareness, to efforts to disseminate science-based oral health information to specific populations, to health information outreach initiatives targeting high school students, to efforts to disseminate science-based information on obesity and diabetes, and to a new, decade-long program devoted to environmental public health. They 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 Sudden Infant Death Syndrome (SIDS), or they may be oriented toward a particular health disparities population subgroup, or both. These include a variety of NIH health information Web sites, several of which are available in Spanish.[413]

NIH outreach also is tailored to meet the needs of specific groups or those who provide treatment or services to a group. Science-based oral health information disseminated by two NIH programs illustrates this point. A Spanish-language Web site increases access to science-based oral health information among Hispanics. The site was tested in two cities to ensure that it is understandable, credible, and attractive to the intended audience of Spanish-dominant and bilingual Hispanics from different countries of origin and with varying levels of education. Dentists, dental hygienists, and caregivers have learned how to better serve the oral health needs of people with developmental disabilities through an online continuing education (CE) program called Practical Oral Care for People with Developmental Disabilities. The modules have proven so popular that NIH extended the CE credit through 2011.

The National Diabetes Education Program (NDEP [http://ndep.nih.gov/]) and the National Kidney Disease Education Program (NKDEP [http://nkdep.nih.gov/]) disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take “small steps” to prevent type 2 diabetes. The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to help coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups at high risk. The Weight-control Information Network (WIN [http://win.niddk.nih.gov/]) provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues. WIN provides tailored information to high-risk groups,

[413] For more information, see http://www.cancer.gov/espanol, http://medlineplus.gov/spanish/, http://aidsinfo.nih.gov/infoSIDA/, http://ndep.nih.gov/, http://win.niddk.nih.gov/, and www.nia.nih.gov/espanol.

such as through the *Sisters Together Program Guide: Move More, Eat Better*, which is tailored for African American women.

In the spring of 2011, the NIH Associate Director of Research on Women's Health was the spokesperson for nation-wide radio media tour entitled, "Understanding Family Health History/Preventing type 2 Diabetes in Women with a History of Gestational Diabetes." The goal of the tour was to raise awareness of risks and prevention strategies for gestational diabetes mellitus (GDM). It reached over one million listeners and pieces were aired on over 200 stations and network affiliates. The tour focused on radio stations and geographic areas with large minority populations, including statewide stations in North Carolina and Tennessee, and the top-rated stations in northern California; St. Louis, Missouri; Dallas-Ft. Worth, Texas; and Denver, Colorado.

Chapter 4

Centers of Excellence

Alzheimer's Disease Centers

Establishment of the Alzheimer's Disease Centers

Based on concerns about the enormity of the problems posed by Alzheimer's disease, Congress directed NIH to foster further research related to Alzheimer's disease (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 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 (see 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, usually mild, behavioral or cognitive changes; these 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 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 also can 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 also are 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—might increase the risk for AD. Increasing evidence also suggests that physical, mental, and social activities may help to 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

Recent estimates from a nationally representative sample in the Aging, Demographics, and Memory Study (part of the ongoing NIH-supported Health and Retirement Study) suggest that one in seven Americans age 72 or older has dementia and about 2.4 million have AD. Other investigators, using projections from community-based studies, estimate that 5.1 million Americans ages 65 or older have AD. Despite the differing methodologies and results of their studies, experts agree that the number of people with AD will increase significantly if current U.S. demographic trends continue and no effectiveprevention methods emerge. 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 ages 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 85 years of age or older.

Scope of NIH Activities: Research and Programmatic

The ADC program provides infrastructure and core resources to enhance ongoing research by bringing together basic biomedical, behavioral and 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 all ADCs to contain administrative, clinical, data management and statistics, education and information transfer, and neuropathology components, known as “cores,” and some Centers support other cores providing specialized resources such as neuroimaging or genetic data. The eleven Alzheimer’s Disease Core Centers provide investigators within and outside the ADC program with access to the broad spectrum of ADC resources, while 16 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 from underrepresented groups.

Resources shared among ADCs include brain and specimen banks at each center, which consist of well-characterized specimens collected under standardized protocols; ADCs have provided biological samples from patients with AD for hundreds of non-ADC funded projects.

A major resource shared by the ADCs is the National Cell Repository for Alzheimer's Disease (NCRAD) at Indiana University, which collects and stores blood, DNA, and cell lines from families with several members affected by AD and from unaffected control participants. NCRAD also stores well-documented phenotypic data, including age and gender. 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 Alzheimer's disease that are being used to identify the susceptibility and protective genes influencing the onset and progression of late-onset disease. These samples are especially valuable because of the rich associated clinical data also available for each participant.

The ADCs have helped create additional collaborative research resources or projects such as 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 28 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 also have 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 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. They also have 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 also are examining relationships and commonalities between AD and cerebrovascular disease or other neurodegenerative diseases as well as contributions of 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. In this regard, collaborations are underway with the NINDS-supported Udall Parkinson's Disease Centers to examine many overlapping scientific and clinical issues.

Another major objective for the ADCs is to recruit minority 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 18 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 related to specific minority concerns in cooperation with the NIH-supported Research Centers on Minority Aging Research.

All ADCs have Education and Information Transfer Cores (EITCs) that provide research training for new investigators, as well as outreach to the public, including caregivers. EITC efforts also have been redefined recently to facilitate participant recruitment for large scale, national projects such as the NIA 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, 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 minority populations, including non-native English speakers people.

NIH Funding for FY 2010 and FY 2011

NIH funding for the ADCs was $50.55 million in FY 2010 and $49.76 million in FY 2011 for non-ARRA (regular appropriations), and $10,000 in FY 2010 for ARRA appropriations.

FY 2010 and FY 2011 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments for the ADCs include the following examples.

- *National Alzheimer's Coordinating Center (NACC).* In 1999, NIH established NACC to facilitate collaborative research and standardize procedures among the ADCs. NACC developed and maintains a large database of standardized clinical and neuropathological research data collected from each ADC. This database provides a valuable resource to qualified research scientists for both exploratory and explanatory AD research. The data provided by NACC support large studies that use patient samples from ethnically, racially and geographically diverse populations and multiple ADCs. A minimum data set (MDS) 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 (UDS) (725 variables) has been collected from over 25,000 subjects enrolled since 2005. Data collected by NACC is freely available for all scientists to use in research studies. 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.

- *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. Moreover, the ADCS mission also includes the design of new instruments for use in clinical studies and the development of novel and innovative approaches to clinical study design and AD clinical study analyses.

In 2012, the ADCS renewal application will be submitted and reviewed. Building on recent exciting discoveries from the Alzheimer's Disease Neuroimaging Initiative, the ADCS will focus on new trial approaches using imaging and other biomarkers in cerebrospinal fluid and plasma to identify participants with AD pathology and to track disease progression and treatment response. ADCS investigators will also place an increased emphasis on prevention studies, particularly in at-risk but presymptomatic individuals.

- *Alzheimer's Disease Neuroimaging Initiative (ADNI).* Most ADCs participate in ADNI, which is an innovative public-private partnership that is examining the potential of serial MRI, PET, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and AD. As is true of the ADCS, the activities and outcomes of ADNI are inextricable from those of the ADCs. ADNI completed the first enrollment phase in August 2007 and now is monitoring the 823 participants using MRI and PET imaging and laboratory and cognitive tests. This 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, Recovery Act funding enabled the ADNI study to move into the "ADNI GO" phase. The ADNI GO research effort is the first 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 is rapidly moving into a third phase, known as "ADNI 2," which has built 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. Topics have ranged from the disease's biology to its family and societal impact, as well as many studies of diagnosis and treatment.

Research accomplishments include the following important recent studies carried out by ADC scientists, which highlight research on biomarkers and AD recently carried out by several centers. These studies are only a few examples from a wide spectrum of research studies conducted by the ADCs.

- *Cerebrospinal Fluid Biomarkers.*[6] NIH-supported researchers, including investigators with the Alzheimer's Disease Neuroimaging Initiative, established a method and standard for testing levels of two candidate biomarkers for AD—tau and beta amyloid proteins. The researchers now have correlated levels of these proteins in CSF with changes in cognition over time and determined that changes in these two protein levels in CSF may signal the onset of mild AD. This is a significant step forward in 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 the NIA and the Alzheimer's Association). The update offers a new paradigm for Alzheimer's, covering the disease as it gradually progresses over many years, from the earliest preclinical, pre-symptomatic 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 due to 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, or GWAS, ever conducted in Alzheimer's research, ADGC investigators confirmed that the gene variant BIN 1 affects development of late-onset Alzheimer's, and identified genetic variants significant for Alzheimer's at EPHA 1, MS4A, CD2AP, and CD33.[414] The genes identified by this study may implicate pathways involved in inflammation, movement of proteins within cells, and lipid transport as being important in the disease process.

- *Beta Amyloid Production and Clearance.* In Alzheimer's disease, a protein fragment called beta-amyloid accumulates at abnormally high levels in the brain. 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.

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 2013.

[414] Naj AC, et al. *Nature Genetics*. 2011;43(5):436–41. PMID: 21460841.

Future Directions

NIH plans for the ADCs to continue to emphasize research related to the transition from normal aging to mild cognitive impairment and to full-blown AD, as well as on 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.

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

Institution and Location	Year Established
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

Older Americans Independence Centers of Excellence

Establishment of the Claude D. Pepper Older Americans Independence Centers

In 1955, the Surgeon General of the United States established five Geriatric Research and Training Centers to advance research on the health care problems of the elderly and 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) to honor former Florida Senator and Representative Claude Denson Pepper for his efforts 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 targets a total of 12 OAICs for funding (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-bing of older adults. Aging research focuses on a range of conditions, including geriatric syndromes (e.g., involuntary weight loss, dizziness, 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, over 40 million Americans are older than 65 years. Of these, nearly 6 million are older than 85, and over 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, and researchers predict that increased longevity is likely to require more financing from federal health care systems, including Medicare and Medicaid. 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 greater independence for older persons, and offer opportunities for training and career development in aging research for young scientists. The program's ultimate goal is to enhance translation of basic and developmental research on aging to applications and interventions that increase or maintain independence for older persons.

NIH expects each OAIC, in its selected area of focus, to:

- Provide intellectual leadership and innovation in geriatrics;
- Stimulate translation of basic and clinical research in aging;
- Facilitate and develop novel multidisciplinary and interdisciplinary research strategies to address current issues in geriatrics care;
- Stimulate incorporation of emerging technologies, methods, and scientific advances into research designs;
- Serve as a source of advice and collaboration to other institutions regarding technology, methodology, analysis, or other expertise relevant to research in aging; and
- Provide research training and career development for future leaders in geriatrics research.

NIH Funding for FY 2010 and FY 2011

NIH funding for the OAICs was $13.97 million in FY 2010 and $13.34 million in FY 2011 for non-ARRA (regular appropriations), and $0.21 million for ARRA appropriations.

FY 2010 and FY 2011 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 Clinic. This Center 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 Center is currently conducting several studies of exercise and other interventions to improve balance and mobility in individuals with chronic low back pain and/or arthritis.

- The theme of the *Duke University OAIC* is to understand and modify different causes of decline in physical functioning. The Duke OAIC develops and evaluates interventions designed to help older Americans prepare for, cope with, and recover from disability arising from late-life disease and aging.

- 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. Recently, Center investigators reported that the drug losartan, commonly used to treat high blood pressure, may be an effective treatment for loss of muscle mass and strength in older adults.

- The *University of California, Los Angeles OAIC* supports the development and testing of interventions to prevent disability. The center emphasizes research that bridges basic biomedical and clinical science. Current projects are addressing the underlying causes of bone loss in osteoporosis and the effects of stroke on nerve-repair genes in the aged brain.

- 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 disease. The Center plans to translate these findings into effective community-based rehabilitation programs.

- Research at the *University of Texas Medical Branch--Galveston OAIC* focuses on age-related sarcopenia and its contribution to loss of independence in older persons.

- The *Wake Forest University OAIC's* mission is to assess the risk factors of 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 theme is the investigation of geriatric health conditions that have several causes. This focus includes single conditions resulting from several contributing factors or affecting several outcomes, and 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. Recent findings from the Michigan OAIC suggest that the proportion of certain inflammatory cells in visceral fat increases with age, which may explain why age-related weight gain has been associated with chronic inflammatory disease.
- 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* is collaborating with the University of Oklahoma Health Sciences Center as the most recently established Center. This Center 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.

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 non-competing renewal process. In addition, each OAIC is required on a yearly basis to convene an external advisory board of expert scientists 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 the progress in key areas of aging research in order to discover new and effective ways to promote healthy and productive aging.

Table 4-2. Claude D. Pepper Older Americans Independence Centers (OAICs)

Institution and Location	Year Established
Duke University, Durham, NC	1955
University of Michigan, Ann Arbor, MI	1989
University of California, Los Angeles, CA	1991

Institution and Location	Year Established
Wake Forest University, Winston-Salem, NC	1991
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994
University of Texas Medical Branch, Galveston, TX	1999
Johns Hopkins University, Baltimore, MD	2003
University of Pittsburgh, Pittsburgh, PA	2004
University of Florida, Gainesville, FL	2007
Boston University, Boston, MA	2008
Mt. Sinai Medical Center, New York, NY	2010
University of Arkansas for Medical Sciences, Little Rock, AR	2011

Muscular Dystrophy Cooperative Research Centers

Establishment of the Wellstone Muscular Dystrophy Cooperative Research Centers

The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (the MD-CARE Act, Pub, L. No. 107-84) included provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for muscular dystrophy research. Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs) in the Omnibus Appropriations for FY 2004 (Public Law 108-199) 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 (see Table 4-3). NHLBI also has co-sponsored the two most recent competitions for Wellstone MDCRCs, co-funds one Center, and plans to support projects within future Wellstone MDCRCs, if NIH receives fundable applications that address NHLBI's mission.

A Steering Committee, consisting of directors and co-directors of each center and NIH science officers, 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, whereas others usually do not appear until 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 lack 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 does 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 body systems in addition to skeletal muscles, 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, 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 (CMD).* 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 affected in addition to muscles.

- *Limb-girdle muscular dystrophies (LGMDs).* All LGMDs show a similar distribution of muscle weakness, affecting both upper arms and legs. Scientists have identified many forms of LGMDs; some affect children, whereas 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 against 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 using cells and animals. Clinical trials of some therapies have begun, including the use of drugs to reduce muscle damage, approaches to increase muscle mass by stopping the activity of other proteins that inhibit muscle growth, and strategies to bypass mutations that cause disease.

Burden of Illness

DMD and BMD affect 1 in 3,500 to 1 in 5,000 boys, respectively. With more than 4 million annual births in the U.S., about 400 to 600 boys are born with DMD or BMD every year.[415] Myotonic dystrophy affects approximately 1 in 8,000 people worldwide,[416] whereas FSHD affects approximately 1 in 20,000 people and affects men and women equally.[417]

[415] For more information, see http://www.cdc.gov/ncbddd/musculardystrophy/data.html.
[416] For more information, see http://ghr.nlm.nih.gov/condition/myotonic-dystrophy.
[417] For more information, see www.nlm.nih.gov/medlineplus/ency/article/000707.htm.

The MD-CARE Act called for the CDC to collect and analyze information on the number, incidence, correlates, and symptoms of individuals with muscular dystrophy. Results from the project described the delay between the start of symptoms and definitive diagnosis of DMD.

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 test interventions in people. The overall focus of the Wellstone MDCRCs is to integrate activities to develop therapies for muscular dystrophies. An open competition led to one new Wellstone MDCRC in 2010, and the renewal of two that had received funds from the FY 2005 competition.

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 2010 and FY 2011 follow.

- At the *University of Rochester* center, researchers are examining cellular and molecular factors that contribute to myotonic dystrophy and testing potential treatments.
- The Washington, D.C., *Children's National Medical Center,* for which funding ended in FY 2010, focused on genetic and cellular factors that contribute to DMD's progression and patient responses to treatment.
- Research at the *University of Iowa* center focuses on understanding the causes 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 involving the University of Chicago, the University of Florida and the University of California, Los Angeles. The projects of this center 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 the involvement of inflammation in this process. These studies could lead to novel strategies for the treatment of many different forms of dystrophy.
- Ongoing research at the *Boston Biomedical Research Institute* center seeks to identify specific biomarkers for FSHD. The Wellstone MDCRC is establishing muscle tissue and cell repository biomarker databases as resources for research and evaluation of clinical trials outcomes.
- Ongoing research at the *University of North Carolina at Chapel Hill* center is 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 testing methods for delivering therapeutic genes to muscle through veins in the legs and arms.

- Established in FY 2010, the Wellstone MDCRC at *Nationwide Children's Hospital* in Columbus, Ohio, is developing methods to overcome immune barriers to gene correction for DMD.

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, and assistance with gene therapy development and production. The Wellstone MDCRC program also supports facilities and personnel for testing candidate therapies in mice and dogs.

NIH Funding for FY 2010 and FY 2011

NIH funding for the Wellstone MDCRC program was $9.10 million in FY 2010 and $9.00 million in FY 2011.

FY 2010 and FY 2011 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments in FY 2010 and FY 2011 include establishing a new Wellstone MDCRC at the *Nationwide Children's Hospital,* Columbus, Ohio, in FY 2010. In addition, the Wellstone MDCRCs at the *University of Iowa* and *University of Pennsylvania* competed successfully for renewal through FY 2015. The *Children's National Medical Center* Wellstone MDCRC, funded under an earlier Wellstone competition, ended its formal center program in FY 2010. However, many of the center's investigators continue to conduct muscular dystrophy research with support from other grants, including a Center for Research Translation award from NIAMS. Moreover, Children's National Medical Center still is 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 additional support from, companies such as PTC Therapeutics and Insmed. The centers also have strong ties with patient advocacy groups and voluntary health organizations that promote and support muscular dystrophy research. These organizations are integral to the success of the Wellstone MDCRCs; they provide advice, assist with patient recruitment, and enhance the research through additional support. The synergy created by NIH resources and the involvement of industry and advocacy groups is accelerating progress toward muscular dystrophy treatments.

Because training and career development is an important component of the Wellstone MDCRC program, all current centers have formal training and education cores. These facilities provide stipends to predoctoral and postdoctoral researchers and enhance the programs' educational environments.

Wellstone MDCRCs have leveraged other NIH funding in muscular dystrophy. In addition to awards reported in prior biennial reports, an NIH institutional training grant in neuromuscular disease has been awarded to investigators at *Nationwide Children's Hospital.* Investigators participating in the *University of Pennsylvania* Wellstone MDCRC received an NIH program project grant for examining the mechanisms and potential therapeutics for muscular dystrophy-associated muscle fibrosis.

The Wellstone MDCRC core facilities are national resources for the muscular dystrophy research community. These facilities have been publicized at national meetings and through center Web sites and the Wellstone MDCRC Web site.[418] These shared research tools foster collaborations across departments or schools within institutions, and among investigators and health care providers nationwide. Examples of these facilities include:

- The *University of Rochester* established the *Repository and National Registry of Myotonic Dystrophy Patients and Family Members* when NIH renewed the center's funding in FY 2008. The facility, a combination of the center's existing Tissue Repository Core and the NIH-funded Registry of Myotonic Dystrophy Patients and Family Members, provides researchers with cell or tissue samples and clinical information about the donors of these samples.[419]

- 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 that have been 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 for center investigators and other academic and industrial researchers. The facility's staff conduct measurements that now are the standard for showing whether a new treatment is effective in animals.

- The MDCRC at the *University of North Carolina at Chapel Hill* launched the *National Vector Muscular Dystrophy Core* in FY 2008. The Core is producing and testing gene therapy materials for researchers.[420] As tests are completed successfully, the facility will supply investigators with materials that they can use for clinical research. The core also will help investigators submit documents to regulatory agencies (such as the U.S. FDA) and comply with all relevant regulations.

Research Activities and Outcomes

The Wellstone MDCRCs conduct basic, translational, and clinical studies related to a variety of muscular dystrophies. Examples of accomplishments in FY 2010 and FY 2011 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. In collaboration with PTC Therapeutics, they have identified chemical scaffolds with activity in increasing muscleblind 1 protein to address the pathophysiological mechanisms in the disease. Also, these investigators have shown preclinical efficacy of antisense oligonucleotides in

[418] For more information, see http://www.wellstonemdcenters.nih.gov/index.htm.
[419] Lemmers RJ, et al. *Science.* 2010;329(5999):1650–3. PMID: 20724583.
[420] Phillips JL, et al. *Methods Mol Biol.* 2011;709:141–51. PMID: 21194026.

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 an NINDS translational cooperative agreement. In clinical studies, the Rochester MDCRC has developed a simpler, less invasive muscle biopsy technique to serve as a molecular surrogate to evaluate candidate therapeutic efficacy in early stage human clinical trials. Their natural history studies of progression of myotonic dystrophy in patients have developed and incorporated new measures (including quality of life measures) and collected longitudinal data that will be essential in designing studies, stratifying subjects, and assessing outcomes in interventional clinical trials.[421]

- 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). After conducting pilot studies in DMD patients with support from the Wellstone MDCRC, these investigators are now collaborating with researchers at Oregon Health and Sciences University and Children's Hospital Philadelphia in a larger study comparing MRI/S and measures of skeletal muscle function in 100 DMD boys and 50 healthy controls. This larger study called ImagingDMD[422] is supported by NIAMS and NINDS. Through the Wellstone MDCRC, new methods are being explored to non-invasively measure muscle scaring and replacement by fat in various forms of dystrophy.

- The *University of Iowa* MDCRC has led important breakthroughs in the molecular mechanisms of the dystroglycanopathies, a class of muscular dystrophy where understanding has lagged until the focused efforts of the Iowa group.[423] The Iowa MDCRC leveraged new therapeutic strategies for drug development that are being explored in an NIH ARRA award that has developed *in vitro* animal models for drug testing and identified putative drug scaffolds through a high throughput screening program. The Iowa MDCRC also is 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 *University of North Carolina at Chapel Hill* Wellstone MDCRC have developed a new method for delivery of fluids through veins to skeletal muscles in the legs of dystrophy patients that is safe and well tolerated. Previously, they showed that this is an effective method for delivery of therapeutic genes in a dog model of DMD. Ongoing studies are preparing for future clinical trials of therapeutic genes to be delivered through the veins to muscles of the arms and legs of dystrophy patients. Researchers at the *Nationwide Children's Hospital* Wellstone MDCRC are preparing to conduct a clinical trial of a gene transfer approach directly into the muscles of DMD patients, and to test methods for minimizing the immune responses.

[421] Hilbert JE, et al. *Contemp Clin Trials.* 2012;33(2):302–11. PMID: 22155025.
[422] For more information, see http://www.imagingdmd.org.
[423] Inamori K, et al. *Science.* 2012:335(6064):93–6. PMID: 22223806.

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 with scientists elsewhere that address key issues in muscular dystrophy and its potential to serve as a national infrastructure and training resource. NIH responded to the burgeoning number of basic research findings in muscular dystrophy by changing the focus of the last two Wellstone MDCRC competitions (FY 2008 and FY 2010) to encourage research that translates basic findings about the disease to human studies and applications in the clinic. To further capitalize on NIH basic and translational research investments and accelerate progress toward effective treatments or other improvements in patients' lives, the next round of centers[424] will be expected to involve clinical research with direct interactions between researchers and muscular dystrophy patients. In addition to therapy development, NIH will also encourage studies of the natural history of diseases, biomarker identification and validation, biopsychosocial studies, and other patient-oriented research. Centers may also contain 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 the progress of each center 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 six outstanding Wellstone MDCRCs. The agency issued three five-year awards to the Wellstone MDCRC program in FY 2010. In FY 2013, NIH plans to hold an open competition and intends to fund up to three Centers (for a total of up to six active Centers), pending the availability of funds.[425] Grantees will join the network of Wellstone MDCRCs to translate scientific findings and technological developments into treatments for muscular dystrophies.

NIH supports multi-project grants and core centers for muscular dystrophy research at academic institutions, in addition to the Wellstone Centers. The agency also is promoting interactions among investigators at the Wellstone Centers and these other institutions to expand the scope and strength of the Wellstone Network.

Table 4-3. Active Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs), FY 2010–2011

Institution and Location	Years active
University of Rochester, Rochester, NY	2003 -present
Children's National Medical Center, Washington, DC	2005 - 2010
University of Iowa, Iowa City, IA	2005 - present

[424] For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-AR-13-002.html.
[425] For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-AR-13-002.html.

Institution and Location	Years active
University of Pennsylvania, Philadelphia, PA	2005 - present
Boston Biomedical Research Institute, 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 Minority Health and Health Disparities Research and Education Act of 2000 (Pub. L. No. 106-525) included provisions for the creation of NCMHD to conduct and support research, training, and dissemination of information with respect to minority health conditions and other populations with health disparities. The statute specifically mandated establishing COEs in research institutions for the purpose of conducting biomedical and behavioral health disparities research and training. In FY 2010, the NCMHD was re-designated the NIMHD, and all the responsibilities of the NCMHD authorized under Public Law 106-525 were transferred to the Institute in accordance with the Patient Protection and Affordable Care Act (Public Law 111-148).

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. These population groups are African Americans, American Indians, Alaska Natives, Asian Americans, Hispanic Americans, Native Hawaiians, and Pacific Islanders, subpopulations of all of these racial/ethnic groups, socioeconomically disadvantaged individuals, and medically underserved populations residing in rural areas.

The COE program supported by the National Institute on Minority Health and Health Disparities (NIMHD), formerly the National Center on Minority Health and Health Disparities (NCMHD) is one of several programs that are central to NIH's scientific investment strategy for addressing and ultimately eliminating health disparities. That strategy encompasses:

- Conducting and supporting basic, clinical, social sciences, health services, and behavioral research;
- Promoting enhancement of research infrastructure and research training; and
- Community engagement and disseminating research information to racial and ethnic minority and other communities that experience health disparities.

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 COE program supports the Department of Health and Human Services Action Plan to Reduce Racial and Ethnic Health Disparities and the National Prevention Strategy.

Since 2002, NIMHD has established COEs in 35 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands (see Table 4-4). Initially, the program used three different funding mechanisms for

Resource-Related Centers (R-24), Exploratory Centers (P20), and Comprehensive Centers (P60). The use of 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 nation's geographically and culturally diverse institutions that have longstanding partnerships with local and regional health disparity organizations and communities. The Resource-Related Centers 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 an NIMHD COE using the Exploratory Centers mechanism.

NIMHD supported 51 COEs in FY 2010 and FY 2011 and all COEs funded since 2005 have had project periods of five years. The types of institutions funded directly by the NIMHD COE program or through partnerships with NIMHD COEs include research-intensive institutions, medical schools, historically black colleges and universities, Hispanic-serving institutions, tribal colleges/universities, and liberal arts colleges. NIMHD COEs have also been successful in developing novel partnerships with different types of non-academic institutions, such as community-based organizations or foundations. These partnerships provide a means for non-academic institutions to engage in the 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. As described in various solicitations published in the *NIH Guide for Grants and Contracts*, the NIMHD COEs conduct research on health disparities associated with the following priority diseases and conditions: cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity. The NIMHD COE program also supports research on lung disease, liver disease, psoriasis, scleroderma, and glomerular (kidney) injury; all of these diseases and conditions disproportionately affect racial and ethnic minorities.

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 diminished by the disproportionate burden of disease and illness and the reduced access to quality health care that racial and ethnic minority populations and the rural and urban poor experience. Compelling evidence of the disparate health status of America's racial and ethnic minority and economically disadvantaged populations includes their shorter life expectancies and higher rates of cancer, birth defects, developmental disorders, infant mortality, asthma, diabetes, obesity, cardiovascular disease, and stroke. Racial and ethnic minorities and the medically underserved also suffer a disproportionate burden of morbidity and mortality associated with HIV/AIDS, autoimmune diseases (such as lupus and scleroderma), 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, research capacity (including training and education), and community outreach. This broad scope provides considerable flexibility for COEs to design and implement multi- and transdisciplinary strategies, studies, interventions, and activities needed for reducing and ultimately eliminating health disparities.

The NIMHD COE program requires all COEs to establish mandatory 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 2010 and FY 2011

NIH funding for the NIMHD COE program was $67.9 million in FY 2010 and $68.8 million in FY 2011. In FY 2011, in partnership with the EPA, funding of $5 million enabled 10 NIMHD COEs to establish research programs for addressing environmental factors contributing to health disparities.

FY 2010 and FY 2011 Progress Report

Programmatic Activities and Outcomes

Significant programmatic accomplishments included establishing four new COEs and one competing renewal. The number of active NIMHD COEs was 51 in FY 2010 and FY 2011 (see Table 4.4).

- In FY 2010, administrative supplements to support bioethics were made available through the NIH Office of the Director. Four NIMHD COEs received funding to establish novel research and or research training activities addressing bioethics issues.
- In FY 2011, in partnership with the Environmental Protection Agency (EPA) the scope of 10 NIMHD COEs was expanded. The principle objective of the collaborative research effort put forth by EPA and NIMHD is to generate innovative approaches to alleviate environmentally driven health disparities and improve access to healthy environments for vulnerable populations.

Research Activities and Outcomes

Funding for the NIMHD COEs has resulted in several FY 2010 and FY 2011 research accomplishments. The COEs conduct research on minority health and the biologic and non-biologic factors contributing to

health disparities. As shown by the following examples, NIMHD researchers are exploring the role of social and cultural factors in the prevalence of priority diseases and conditions.

The NIMHD Center of Excellence in Eliminating Disparities (CEED) at the University of Illinois, Chicago addresses racial/ethnic disparities through research in cancer prevention, early detection and treatment management. Research conducted by this COE has found that multi-level hierarchical models based on an existing population-based ovarian cancer survival cohort in which disadvantage measures were computed with the 2000 census data, suggest that women living in disadvantaged neighborhoods were more likely to be diagnosed at later stages of ovarian cancer and have shorter survival.

The NIMHD COE program at the University of Montana has established diverse partnerships with seven or more of the tribes in Montana and is engaged in community based participatory research (CBPR) projects. CBPR is a research approach that is preferred by many tribes. One such project has been established to address Apsáalooke (CROW) community cancer risks from contaminated water. This partnership includes Little Big Horn College, the CROW tribe, the Indian Health Service, the Apsáalooke Water and Wastewater Authority, the 107 Committee (of Tribal Elders), Montana State University and the University of New England. This partnership has conducted over 120 well surveys.

Collaborations between NIMHD COEs and Clinical Translation Science Awards (CTSA) and Clinical Translation Science Institutes (CTSI) have been an important part of the success of the COE program. Seventeen (81 percent) of the 21 active NIMHD P60 COE institutions have also received CTSA program funding and several of these institutions are leveraging their joint interests and capabilities in community engagement and outreach and health disparities by establishing partnerships. For example, the NIMHD COE established at the New York University (NYU) Center for the Study of Asian American Health has partnered with the CTSI established by NYU and New York City Health and Hospitals Corporation (HHC). The NIMHD COE and the NYU CTSI have developed the Community-Empowered Research Training (CERT) Program for building research capacity among community organizations and providers interested in conducting community-initiated research.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NIMHD COEs

Since their inception in year 2002, NIMHD COEs made progress toward the elimination of health disparities. However, much more needs 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 need to be more targeted toward interventions that work. As a result of the 2008 NIH Summit to Eliminate Health Disparities and subsequent Funding Opportunity Announcements recognizing and stressing the multifactorial and multidisciplinary nature and complexities of health disparities, NIMHD COEs established in 2010 have placed emphasis on research and interventions addressing the social determinants of health. NIMHD and its COEs cannot and are not acting alone; NIMHD has sought and continues to seek new partners and also encourages each NIMHD COE to establish partnerships with other NIH-funded centers and programs, other federal agencies, and others committed to eliminating health disparities. The partnerships established with other federal agencies in FY 2010 and FY 2011 expanded the scope of research and research activities

conducted by NIMHD COEs. In FY 2012, NIMHD will continue to pursue the recommendations previously published in the 2008-2009 Biennial Report:

- Establish partnerships with other NIH-funded centers and programs, other federal agencies, and others committed to eliminating health disparities as a way to maximize resources.
- Increase the diversity of the scientific workforce, especially the number of women and biomedical and behavioral scientists from racial/ethnic and other health disparity populations. Focused efforts are especially needed to increase the number of women 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 address more effectively the transdisciplinary challenges in health disparities elimination and prevention research.
- Enhance the nation's research capacity to conduct health disparities research by expanding the research and training opportunities available.

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); training of junior faculty from health disparity populations, postdoctoral fellows, and graduate and undergraduate students; and K–12 educational efforts. This review ascertains the COE's progress in meeting the aims and objectives of the grant and assists in identifying areas of concern that need to be addressed. The Office of Minority Health, HHS, will assist the NIMHD in evaluating the effectiveness of the NIMHD COEs funded to promote patient–centered outcome research.

Future Directions

The NIMHD COE program will continue to intensify research efforts to understand, reduce, and eliminate health disparities, with an emphasis on sustaining current partnerships and establishing new ones. The 2012 Summit on the Science of Eliminating Health Disparities involved agencies across the federal government and resulted in several new partnerships for the NIMHD and for the NIMHD COEs and several significant recommendations for future research themes. With the establishment of new partnerships, NIMHD expects that its COEs will continue to discover new biomedical and behavioral knowledge for improving minority health and eliminating health disparities within and across the priority areas of cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity, as well as in lung and liver diseases, psoriasis, scleroderma, and glomerular injury. It

is also expected that NIMHD COEs will embrace future research themes that will expand beyond these areas to include research recognizing and integrating the environmental sciences, bioethics, social and political sciences, and policy with translational practices and interventions to build a healthier society.

The COEs also will 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 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 disentangling the contribution to health disparities of biologic, behavioral, and social factors, and health policies and practices. Conducting population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the United States (especially the Mississippi Delta, Appalachia, the U.S.-Mexico border region, and tribal communities) will continue to be important. NIMHD will continue to support studies to eliminate or decrease the impact of factors, including natural disasters, that contribute to the excess risks, morbidity, and mortality associated with living in these regions.

Table 4-4. NIMHD Centers of Excellence Active in FY 2010 and FY 2011

Institution and Location
Arizona State University, Tempe, AZ
Case Western Reserve University, Cleveland, OH
Charles R. Drew University of Medicine & Science, Los Angeles, CA
Clark Atlanta University, Atlanta, GA
Columbia University Health Sciences, New York, NY
Dillard University, New Orleans, LA
Florida International University, Miami, FL
Georgia State University, Atlanta, GA
Howard University, Washington, DC
Johns Hopkins University, Baltimore, MD
Medical College of Georgia, Augusta, GA
Meharry Medical College, Nashville, TN
Montana State University, Bozeman, MT
Mount Sinai School of Medicine of NYU, New York, NY

Institution and Location
New York University School of Medicine, New York, NY
North Carolina Central University, Durham, NC
San Diego State University, San Diego, CA
State University of Albany, Albany, NY
Texas A&M University System, College Station, TX
Uniformed Services University of the Health Sciences, Bethesda, MD
University of Alabama, Birmingham, AL
University of Arkansas Medical Sciences, Little Rock, AR
University of California, San Diego, CA
University of Colorado Denver and Health Sciences Center, Aurora, CO
University of Hawaii, Manoa, HI
University of Illinois, Chicago, IL
University of Kansas Medical Center, Kansas City, KS
University of Maryland, College Park, MD*
University of Massachusetts, Boston, MA
University of Miami, Coral Gables, FL
University of Michigan, Ann Arbor, MI
University of Minnesota, Twin Cities, MN
University of New Mexico, Albuquerque, NM
University of North Carolina, Chapel Hill, NC
University of North Carolina, Greensboro, NC
University of Oklahoma Health Sciences Center, Oklahoma City, OK
University of Puerto Rico Medical Sciences, San Juan, PR
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 Southern California, Los Angeles, CA

Institution and Location
University of Texas Health Sciences Center, Houston, TX
University of Texas M.D. Anderson Cancer Center, Houston, TX
University of Texas, El Paso, TX
University of the Virgin Islands, St. Thomas, VI
University of Wisconsin, Madison, WI
Virginia Commonwealth University, Richmond, VA
Weill Medical College, Ithaca, NY
Winston-Salem State University, Winston-Salem, NC
Yeshiva University, New York, NY

*Formerly located at the University of Pittsburgh, since 2002.

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 has developed a novel collaborative model of rare disease research in a number of ways including integration of patient advocacy groups as research partners. Its purpose is to facilitate clinical research in rare diseases through support for 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 projects; 4) a test bed for distributed clinical data management that incorporates novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms; and 5) access to information related to rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the lay public.

In February 2008, ORDR, in collaboration with several NIH ICs, opened a re-competition for funding support for the network and the Data Management and Coordinating Center (DMCC). The resulting network consists of 19 consortia and a Data Management Coordinating Center, each with cooperative agreement awards for five years. ORDR is collaborating with NINDS, NIAID, NIAMS, NICHD, NIDCR, NHLBI, NIDDK, and NCI.

The DMCC houses all data for the network centrally via in-house scalable and customizable electronic data capture systems. Some of the data systems built by the DMCC for the RDCRN include a specimen collection, shipment, and tracking system; randomization system; participant management system with electronic case report forms; standardized and automated report sets (accrual, demographics, adverse events, compliance, study status); automated XML/CSV data sets with associated data dictionaries; and an Adverse Event Data Management System for real time reporting, submission, and review of adverse events.

An additional feature, the RDCRN Contact Registry, together with consortia information, is designed for access by the general public [http://www.rarediseasesnetwork.org]. Users access an enrollment form for the Contact Registry via one of 19 consortium-specific web pages. The RDCRN consortia web pages and associated links to the Contact Registry are accessible from disease-specific searches on a variety of internet browsers. 171 diseases are represented by 9,806 registrants. The Contact Registry has been utilized as a pathway for informing registrants about studies. The first instance of this success was a partnership between the DMCC and the Vasculitis Clinical Research Consortium (VCRC) whereby over 500 subjects were recruited and the study was completed within three months.

The DMCC also maintains the public web pages and portals for all consortia within the network. Since August 2009, the public web pages have experienced over 600,000 visits with 515,000 visits occurring in the last 12 months.

Clinical trials and research studies and network collaborations have resulted in 279 publications including one book, nine book chapters, three conference posters, 45 conference papers, two special publications, and 219 journal articles.

How the RDCRN Functions within the NIH Framework

Each consortium develops and, after approval, carries out clinical protocols for a set of related rare diseases with guidance from one or several 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 ICs, and the Chair of the Coalition of Patient Advocacy Groups (CPAG) in the network.

The network's improved infrastructure and functions build on lessons learned in previous years and uses those approaches that have proven to be most effective while searching for additional efficiencies and innovation.

Description of Disease or Condition

A disease is defined as rare if fewer than 200,000 persons in the United States have it. There are more than 6,500 rare diseases for which fewer than 250 treatments have been approved as orphan products, drugs that are specifically developed to treat a rare disease. Approximately 80 percent of rare diseases are thought to be of genetic origin. It is estimated that at least 50 percent of the patients are children. The National Organization for Rare Disorders (NORD) estimates that about 1 in 10 people in the U.S. have a rare disease, which translates to as many as 25 to 30 million people. The 19 consortia below study the listed rare diseases and many others which are listed at the network web site http://rarediseasesnetwork.epi.usf.edu/:

The Angelman, Rett, and Prader-Willi Syndrome Consortium (ARPWSC):

- Angelman,
- Rett
- Prader-Willi Syndrome

The Autonomic Disorders Consortium (ADC):

- Multiple system atrophy (MSA)
- Baroreflex failure
- Autoimmune autonomic neuropathy
- Hypovolemic postural tachycardia syndrome (hPOTS)
- Dopamine beta hydroxylase deficiency (DBHD)

The Brain Vascular Malformation Consortium:

- Familial cavernous malformations (CCM)
- Sturge-Weber syndrome (SWS)
- Hereditary hemorrhagic telangiectasia (HHT)
- Brain arteriovenous malformation (BAVM)

The Chronic Graft vs. Host Disease (GVHD) Consortium:

- Cutaneous sclerosis
- Bronchiolitis obliterans
- Late acute graft versus host disease
- Chronic graft versus host disease

The Clinical Research Consortium for Spinocerebellar Ataxias:

- Spinocerebellar ataxias 1, 2, 3 and 6 (the most common of the 31 under study)
- Ataxia telangiectasia
- Friedreich's ataxia
- Mitochondrial ataxia
- Multiple system atrophy-cerebellar type (MSA-C)
- Sporadic ataxia with varying ages of onset

The Consortium for the Clinical Investigation of Neurologic Channelopathies (CINCH):

- Andersen-Tawil Syndrome (a form of Periodic Paralysis)
- Episodic Ataxias
- Non-dystrophic Myotonic Disorders

The Dystonia Coalition:

- Cervical dystonia
- Blepharospasm
- Spasmodic dysphonia
- Craniofacial dystonia
- Limb dystonia

The Genetic Disorders of Mucociliary Clearance Consortium:

- Primary ciliary dyskinesia (PCD)
- Cystic fibrosis (CF)
- Pseudohypoaldosteronism (PHA)

The Inherited Neuropathies Consortium (INC)

- Charcot Marie Tooth disease (CMT), including CMT1
- CMT2, dominantly inherited axonal neuropathies
- CMT4, recessively inherited neuropathies

The Nephrotic Syndrome Study Network (NEPTUNE):

- Focal and segmental glomerulosclerosis (FSGS)
- Minimal change disease (MCD)
- Membranous nephropathy (MN)

The North American Mitochondrial Disease Consortium (NAMDC)

- AID: Aminoglycoside-induced deafness
- Alpers syndrome
- CoQ deficiency
- Encephalopathy
- Leukoencephalopathy

- Mitochondrial encephalopathy lactic acidosis with stroke-like episodes (MELAS)

The Porphyrias Consortium:

- Acute intermittent porphyria (AIP)
- Hereditary coproporphyria (HCP)
- Aminolevulinate dehydratase deficiency porphyria (ADP)
- Porphyria cutanea tarda (PCT)
- Congenital erythropoietic porphyria (CEP)

The Primary Immune Deficiency (PID) Treatment Consortium (PIDTC)

- Severe combined immunodeficiency (SCID)
- Wiskott-Aldrich syndrome (WAS)
- Chronic granulomatous disease (CGD)

The Rare Kidney Stone Consortium

- Primary hyperoxaluria
- APRT deficiency (Dihydroxyadeninuria)
- Cystinuria
- Dent disease
- Lowe Syndrome

The Salivary Gland Carcinomas Consortium (SGCC):

- Smith-Lemli-Opitz syndrome (SLOS)
- Niemann-Pick disease Type C (NPC)
- Sjögren-Larsson syndrome (SLS)
- Sitosterolemia
- Cerebrotendinous xanthomatosis (CTX)

The Urea Cycle Disorders Consortium

- N-Acetylglutamate synthase (NAGS) deficiency
- Carbamyl phosphate synthetase (CPS) deficiency
- Ornithine transcarbamylase (OTC) deficiency
- Argininosuccinate synthetase deficiency (citrullinemia I)
- Arginase deficiency (hyperargininemia)

The Vasculitis Clinical Research Consortium (VCRC)

- Churg-Strauss Syndrome (CSS)
- Giant cell (temporal) arteritis (GCA)
- Granulomatosis with polyangiitis (Wegener's) (GPA)
- Microscopic polyangiitis (MPA)
- Takayasu's arteritis (TAK)

The Lysosomal Disease Network

- Aspartylglucosaminuria
- Batten disease
- Cystinosis mucopolysaccharidoses (MPS)
- Niemann-Pick disease

- Sanfilippo syndromes

The Sterol and Isoprenoid Diseases Consortium (STAIR)

- Smith-Lemli-Opitz Syndrome
- Sjögren-Larsson Syndrome
- Mevalonate Kinase Deficiency
- Cerebrotendinous Xanthomatosis
- Sitosterolemia

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, all the rare diseases listed above and the others studied are devastating and costly, not only for the patients but also for the family. This is due partly because of the disease severity and partly because diagnosis can take a long time, often occurring well after symptoms have appeared. In addition, often treatment is not available once a disease is diagnosed. Moreover, 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, few drug companies conduct research into rare diseases since it is difficult for them to recover the costs of developing treatments for small, geographically dispersed populations.

Scope of NIH Activities: Research and Programmatic

The RDCRN brings together experts who are skilled in studying, diagnosing, and treating particular groups of rare diseases and who train junior faculty and postgraduate fellows. In addition, the network enables each consortium to gather groups of patients with similar or related disorders, fosters basic scientific investigation and longitudinal natural history and epidemiological studies which in the past have often not been funded, encourages synergy in translational research, and enhances opportunities for collaborative clinical investigation.

NIH Funding for FY 2010 and FY 2011

NIH funding for the RDCRN was $20.80 million for 19 consortia and the DMCC in FY 2010 and $16.60 million in FY 2011. The total cost over five years for the RDCRN's Phase II is estimated to be $117 million.

FY 2010 and FY 2011 Progress Report

Programmatic and Research Activities and Outcomes

The RDCRN is unique in its approach to addressing rare diseases. Previously, the NIH ICs funded research on individual rare diseases in their respective disease-type or organ domain. In the first two years since the second grant cycle of the RDCRN (August 2009 to September 2011), the network has activated 41 multi-site clinical research studies. The Network has 78 active studies which are accruing at over 162 clinical centers; 26 of the enrolling clinical centers are located internationally (with representation from

the United Kingdom, Netherlands, Germany, France, Italy, Spain, Switzerland, Canada, Iceland, and Australia). In addition, 100 trainees were prepared to lead future rare diseases research. Since August 2009, 10 studies have completed accrual and are in the final analysis phase. In addition, a total of 8,329 participants have been enrolled since the beginning of the second grant cycle. The network established a comprehensive training program for clinical investigators and developed a network-wide web site to inform the public, physicians, patients, and investigators about the rare diseases under study. The network's aims continue to include training a cadre of young investigators in the clinical and physiological processes associated with each disease and pharmacologic aspects of specific rare diseases. The network's training includes instruction on and experience with methodologies for patient-oriented clinical research in rare diseases, including biostatistics and epidemiology, and the conceptualization, ethics, design, implementation, analysis, and reporting of controlled clinical trials. An integrated training program provides supervision by clinicians and biostatisticians with extensive experience in investigating rare diseases and developing novel therapies. The training program also provides an integrated statistics, epidemiology, and computer science curriculum; seminars on clinical trial design; courses in the basic sciences underlying experimental therapeutics and in ethics; and career development support.

Findings in recent publications are examples of just a few of the scientific-research accomplishments of the RDCRN:

- Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis (LAM): LAM is a progressive lung disease, primarily in young women. Sirolimus stabilized lung function and was associated with a reduction in symptoms and improvement of life for select patients with LAM.
- Mexilitine is an effective therapy in improving symptoms and signs of myotonia in patients with non-dystrophic myotonia.
- N-carbamylglutamate may serve as an important therapeutic adjunct in the treatment of acute hyperammonemia in patients with propionic acidemia. The drug may serve as an important therapeutic adjunct in the treatment of acute hyperammonemia in this disorder.
- Children with neonatal urea cycle defects (UCDs) typically have high mortality and poor neurologic outcomes unless they receive liver transplantations. A study of children with neonatal urea cycle defects concluded that *early* liver transplantation, aggressive metabolic management, and *early* childhood intervention improve the neurologic outcome for children with UCDs.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the RDCRN

Future Directions

ORDR and its partner NIH Institutes will develop requirements for the next five-year grant cycle. The requirements will build on the experience and lessons learned in the program's previous years.

Table 4-5. Rare Diseases Clinical Research Network

Institution and Location	Year Established
University of Pennsylvania, Philadelphia, PA (previously 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 Baylor College of Medicine, Houston, TX)	2003
University of Rochester, NY	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 and Sciences University, Portland, OR	2009
University of California, San Francisco, CA (two locations)	2009
University of Florida, Gainesville, FL	2009
University of Michigan at 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, 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 88 children has an ASD. These estimates are based on data collected from health and special education records of children living in 14 areas of the U.S. during 2008..[426] NIH is working to better understand the causes of autism spectrum disorder and 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 autism spectrum disorder. In response to the Combating Autism Act, the NIH Autism Coordinating Committee formed the Autism Centers of Excellence (ACE) program by consolidating the aims of two previous autism spectrum disorder research programs into a single research effort. The previous programs were 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). The ACE program, funding of which began in FY 2007 and FY 2008, focuses on identifying the causes of autism spectrum disorder and developing new and improved treatments.

How the Autism Centers of Excellence Function within the NIH Framework

A key feature of the Combating Autism Act was expanding the scope of the Interagency Autism Coordinating Committee (IACC), initially established by the Children's Health Act of 2000. The IACC includes federal agency representatives and members of the public appointed by the Secretary of HHS. In accordance with the 2006 law, and as re-authorized under the Combating Autism Reauthorization Act of 2011, the IACC develops and updates annually a strategic plan for autism spectrum disorder research and a summary of autism spectrum disorder research advances. The first edition of the plan was released in 2009, and annual updates were released in 2010 and 2011. Though the ACE program was initiated prior to completion of the first IACC Strategic Plan, ACE activities address many identified priority areas, including biomarkers, genetic susceptibility, pharmacological treatments, early intervention, and risk and protective factors.

The ACE program comprises five centers and six 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 sub-projects. 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 autism spectrum disorder, achieving optimal design for treatment trials.

[426] Autism and Developmental Disabilities Monitoring Network (CDC). Prevalence of Autism Spectrum Disorders — Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States 2008. *MMWR*. 2012/61(SS03);1–19. PMID: 22456193.

The goals of the ACE program were established by the NIH ACC—a working group composed of the seven NIH Institutes (NIMH, NICHD, NIDCD, NINDS, NIEHS, NINR, & NCCAM) that support autism spectrum disorder research and are tasked with enhancing the quality, pace, and coordination of research efforts at the NIH in order to find a cure for autism. Five of the ACC ICs provide funding to the ACE program (NIMH, NICHD, NIEHS, NINDS, & NIDCD), and these ICs 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."[427] 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 stereotyped behavior patterns. "Classic" autistic disorder is the most disabling; other forms of autism spectrum disorder, such as Aspergers disorder, have fewer or milder symptoms. Intellectual disabilities, seizures, and self-abusive behaviors are common among children at the more severe end of the spectrum.

A child's primary caregivers often are the first to identify autism spectrum disorder symptoms. As early as infancy, a baby with autism spectrum disorder may be unresponsive to people or focus intently on one item to the exclusion of others for long periods. A child with autism spectrum disorder may appear to develop normally and then withdraw and become indifferent to social engagement. Clinicians can make a reliable autism spectrum disorder diagnosis for most children by age three. The current autism spectrum disorder 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 were more narrowly defined than they are today.

Burden of Illness

Autism spectrum disorder causes tremendous economic and social burdens for families and society at large. Although autism spectrum disorder 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 autism spectrum disorder might receive private and public services in special education settings, hospitals, university medical centers, or residential treatment facilities, among others.

Some scientists and economists have estimated that the combined direct and indirect costs of providing care for all Americans with autism spectrum disorder during their lifetimes exceed $34 billion. The estimated costs over a lifetime for each person total $3 million.[428] Families often incur large debts for

[427] Kanner L. *Nerv Child.* 1943;2:217–50.
[428] Ganz ML. *Arch Pediatr Adolesc Med.* 2007;161(4):343–9. PMID: 17404130.

medical and education services that public programs or medical insurance do not cover. In addition, autism spectrum disorder often leads to profound emotional hardships for patients and their families. However, the Affordable Care Act will help ease the financial burden that often comes with treating and caring for people with autism spectrum disorder. The law requires new plans to cover autism screening and developmental assessments for children at no cost to parents and allows parents to keep their children on their family health insurance until they turn 26. Insurers will also no longer be allowed to deny children coverage for a pre-existing condition such as autism or to set arbitrary lifetime or annual limits on benefits.

Prevalence estimates—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 88 children has autism spectrum disorder.[429] Boys are approximately four times as likely as girls are to have autism spectrum disorder.[430] However, it is unclear if incidence, the number of new cases across time in the same population, also has increased. It also is unclear whether the rise in prevalence is due to such factors as the use of different criteria to diagnose autism spectrum disorder, earlier and more accurate autism spectrum disorder diagnoses, or increases in biologic, environmental, or other risk factors. A similar increase in autism spectrum disorder prevalence has occurred in other countries.

Scope of NIH Activities: Research and Programmatic

The six centers and five networks that compose the ACE program cover a broad range of autism spectrum disorder 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, and a potential new treatment.

In an effort to support and accelerate research in the prevention, cause, diagnosis, and treatment of research on autism spectrum disorder, NIH created the National Database for Autism Research (NDAR), an informatics system and central data repository. NDAR collects a wide range of data types, including phenotypic, clinical, and genomic, as well as de-identified medical images, derived from individuals who participate in autism spectrum disorder research, regardless of the source of funding. NDAR provides the infrastructure to store, search across, retrieve, and analyze these varied types of data.

While NDAR receives data from many public and privately funded research sources, all ACE centers and networks are required to contribute their data to NDAR. NDAR also coordinates data access with other federal databases, such as the NIMH Center for Collaborative Genetic Studies. The center is a national resource for researchers who study the genetics of complex mental disorders, including autism spectrum disorder, and stores human DNA, cell cultures, and clinical data. In 2011, NDAR received an HHS*innovates* award, recognizing its outstanding efforts to accelerate research within the Department.

[429] Autism and Developmental Disabilities Monitoring Network. *MMWR Surveill Summ*. 2012;61(3):1–19. PMID: 22456193.
[430] Fombonne E. *J Clin Psychiatry.* 2005;66 Suppl 10:3–8. PMID: 16401144.

NIH Funding for FY 2010 and FY 2011

Five NIH ICs 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 $25.60 million in FY 2010 and $25.50 million in FY 2011.

FY 2010 and FY 2011 Progress Report

Programmatic and Research Activities and Outcomes

The activities and several accomplishments of the ACE program are highlighted briefly below.

Yale University: Researchers are searching for biomarkers of visual engagement and auditory perception in infants at risk for autism spectrum disorder. Their projects will build upon existing research on the behavioral, brain, and molecular aspects of autism spectrum disorder and may lead to new discoveries on the causes and best treatments for autism spectrum disorder.

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 autism spectrum disorder. They also are 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 autism spectrum disorder and factors that might protect people from developing autism spectrum disorder. Researchers at the University of Washington center conducted a randomized computerized training program for adults with autism spectrum disorder who showed initial impairment in their ability to recognize faces. Their findings suggest that adults with autism spectrum disorder who undergo the computerized training can gain expertise in facial recognition and processing skills.[431]

University of North Carolina 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 autism spectrum disorder. A study from the network found evidence of enlarged portions of the amygdala in 6- to 7-year-old children with autism spectrum disorder and that these differences were associated with deficits in social and communicative behavior.[432]

University of California, San Diego (UCSD): The UCSD ACE is using brain imaging methods to track brain development in children believed to be at risk for autism spectrum disorder. In a recent study, UCSD ACE investigators found that children with autism had 67 percent more neurons in the prefrontal cortex and heavier brains for their age compared to typically developing children. Since these

[431] Faja S, et al. *J Autism Dev Disord.* 2012;42(2):278–93. PMID: 21484517.
[432] Kim JE, et al. *Arch Gen Psychiatry.* 2010;67(11):1187–97. PMID: 21041620.

neurons are produced before birth, the study's findings suggest that differences in prenatal cell birth or maintenance may be involved in the development of autism.[433]

University of California, Los Angeles: Researchers at the ACE are studying the causes and treatments of social communication problems in people with autism spectrum disorder.

University of Pittsburgh: The University of Pittsburgh ACE is studying how people with autism spectrum disorder learn and understand information.

Drexel University: Researchers with the Drexel University network sites are studying possible risk factors and biological indicators of autism spectrum disorder before and soon after birth. This project is part of the Early Autism Risk Longitudinal Investigation (EARLI).

University of California, Davis: Researchers with the UC-Davis network sites are examining factors that might be useful for improving treatment outcomes in very young children with autism. They are comparing an intensive behavioral intervention to standard community-based treatment.

Wayne State University: Investigators with the Wayne State network sites will conduct a clinical trial to test the safety and efficacy of buspirone, a drug that increases the body's production of serotonin—one of several neurotransmitters that brain cells use to communicate with each other—as an early intervention in children younger than six years with autism spectrum disorder. 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: Researchers at the University of California, Los Angeles network sites are studying the relationship between genes related to autism and physical features. They also are investigating rare genetic variations, mutations, and abnormalities that affect a person's risk for autism.

Several investigators across the ACE centers and networks (University of California – Los Angeles, University of Illinois at Chicago, University of Pittsburgh, University of North Carolina at Chapel Hill, Yale University, and University of Washington), contributed both genetic data and analytic expertise to study the genome-wide characteristics of rare copy number variations or genetic mutations that are strongly associated with the risk of autism spectrum disorder. This large study identified both inherited and *de novo* (i.e., spontaneous or induced, not inherited) copy number variations that implicated a number of genes associated with risk of the disorder.[434]

[433] Courchesne E, et al. *JAMA.* 2011;306(18):2001–10. PMID: 22068992.
[434] Pinto D, et al. *Nature.* 2010;466(7304):368–72. PMID: 20531469.

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, the 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 2008-2009, the group initiated a feasibility study to evaluate the ACE program. The objectives of the study were 1) to determine the availability of data and the feasibility of answering key questions about the ACE program, and 2) to obtain baseline data on the ACE program. The key study questions focused on the program's implementation and scientific scope. This included describing the organization and staffing of the ACE centers and networks, the publication and grant history of the ACE investigators, areas of research addressed in the ACE program, leveraging of additional funding sources, and the role of NDAR in the ACE program. The study also collected data on initial outputs resulting from ACE program research, including research publications and science advances, as well as other information to guide plans for future ACE program evaluation activities. Overall, this initial study and future evaluation activities are intended to complement, but not duplicate, the NIH scientific peer review process, which remains the primary means to ensure the scientific excellence of NIH-funded research.

A report addressing the areas outlined above was developed in 2010. Based on the results of the feasibility study, the AEIO has outlined plans to periodically update the baseline data, including plans to update several elements in 2012.

Future Directions

In 2011, as in the prior year, the NIH ACC convened a two-day meeting at which the investigators presented progress towards the goals of their ACE and exchanged ideas for collaborations. Some sessions addressed data sharing options through the 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. Principal investigators were encouraged to invite K award (career development grant) recipients, fellows, and postdoctoral students from their laboratories.

In FY 2011, NIH re-issued the ACE funding announcements (RFA-HD-12-195; RFA-HD-12-196). Applicants were instructed that highest funding priority would be given to projects related to gaps identified by the 2011 IACC Strategic Plan.

Table 4-6. Autism Centers of Excellence (ACEs)

Institution and Location	Year Established
University of California, Davis, CA	2007
University of California, Los Angeles, CA	2007
University of California, San Diego, CA	2007
University of Illinois, Chicago, IL	2007
University of North Carolina, Chapel Hill, NC	2007
University of Pittsburgh, Pittsburgh, PA	2007
University of Washington, Seattle, WA	2007
Yale University, New Haven, CT	2008
Wayne State University, Detroit, MI	2008
University of California, Los Angeles, CA	2008
Drexel University, Philadelphia, PA	2008

Appendix A:
Legal Mandate for This Report

Pub. L. No. 109-482: The National Institutes of Health Reform Act of 2006 (Relevant Provisions)

An Act

To amend title IV of the Public Health Service Act to revise and extend the authorities of the National Institutes of Health, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "National Institutes of Health Reform Act of 2006".

TITLE I—NIH REFORM

- -

SEC. 102. AUTHORITY OF DIRECTOR OF NIH.

- -

(b) ADDITIONAL AUTHORITIES.—Section 402(b) of the Public Health Service Act, as amended by subsection (a) of this section, is amended by striking paragraphs (2) and (3) and inserting the following:

- -

"(7)(A) shall, through the Division of Program Coordination, Planning, and Strategic Initiatives—

" (i) identify research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between 2 or more national research institutes or national centers, or would otherwise benefit from strategic coordination and planning;

"(ii) include information on such research in reports under section 403;

- -

SEC. 104. REPORTS

(a) REPORT OF DIRECTOR OF NIH.—The Public Health Service Act (42 U.S.C. 201 et seq.), as amended by section 103(a) of this Act, is amended—

- -

(3) by striking section 403 and inserting the following sections:

"SEC. 403. BIENNIAL REPORTS OF DIRECTOR OF NIH.

"(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;

"(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.

- -

SEC. 106. ENHANCING THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD.

(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—

- -

(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).

Public Law 110-85: The Food and Drug Administration Act of 2007 (Relevant Provisions)

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the post market authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Amendments Act of 2007."

- -

TITLE XI—OTHER PROVISIONS

Subtitle A—In General

- -

SEC. 1104. NIH TECHNICAL AMENDMENTS.

The Public Health Service Act (42 U.S.C. 201 et seq.) is amended—

- -

(3) in section 403(a)(4)(C)(iv)(III), by inserting "and postdoctoral training funded through research grants" before the semicolon;

Public Law 110-204: The Newborn Screening Saves Lives Act of 2007 (Relevant Provisions)

An Act

To amend the Public Health Service Act to establish grant programs to provide for education and outreach on newborn screening and coordinated follow-up care once newborn screening has been conducted, to reauthorize programs under part A of title XI of such Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This act may be cited as the "Newborn Screening Saves Lives Act of 2007".

- -

SECTION 7. CONTINGENCY PLANNING.

Part A of title XI of the Public Health Service Act (42 U.S.C. 300b-1 et seq.) as amended by section 6, is further amended by adding at the end the following:

- -

"SEC. 1116. HUNTER KELLY RESEARCH PROGRAM.

(a) NEWBORN SCREENING ACTIVITIES. —

"(1) IN GENERAL. —The Secretary , in conjunction with the Director of the National Institutes of Health and taking into consideration the recommendations of the Advisory Committee, may continue carrying out, coordinating, and expanding research in newborn screening (to be known as 'Hunter Kelly Newborn Screening Research Program') including —

- -

"(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 of the National Institutes of Health Reform Act of 2006.

Appendix B:
Priorities and Plans of the Institutes and Centers and the Program Offices in the Office of the Director

This appendix provides links to the 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.

National Cancer Institute (NCI)

- Mission Statement: http://www.cancer.gov/aboutnci/overview/mission
- Strategic Plan: http://strategicplan.nci.nih.gov/

National Heart, Lung, and Blood Institute (NHLBI)

- Mission Statement: http://www.nhlbi.nih.gov/about/org/mission.htm
- Strategic Plan: http://www.nhlbi.nih.gov/about/strategicplan/index.htm?/Default.aspx

National Institute of Dental and Craniofacial Research (NIDCR)

- Mission Statement: http://www.nidcr.nih.gov/AboutUs/MissionandStrategicPlan/MissionStatement/
- Strategic Plan: http://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: http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/default.htm

National Institute of Neurological Disorders and Stroke (NINDS)

- Mission Statement: http://www.ninds.nih.gov/about_ninds/mission.htm
- Strategic Plan: http://www.ninds.nih.gov/about_ninds/plans/NINDS_strategic_plan.htm

National Institute of Allergy and Infectious Diseases (NIAID)

- Mission Statement: http://www.nih.gov/about/almanac/organization/NIAID.htm

- Strategic Plan: http://www.niaid.nih.gov/about/whoweare/planningpriorities/strategicplan/Pages/default.aspx

National Institute of General Medical Sciences (NIGMS)

- Mission Statement: http://www.nigms.nih.gov/research/featuredprograms/PSI/Background/MissionStatement
- Strategic Plan: http://www.nigms.nih.gov/About/StrategicPlan/

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- Mission Statement: http://www.nichd.nih.gov/about/overview/mission/index.cfm
- Strategic Plan: https://www.nichd.nih.gov/publications/pubs/upload/strategicplan.pdf

National Eye Institute (NEI)

- Mission Statement: http://www.nei.nih.gov/about/mission.asp
- Strategic Plan: http://www.nei.nih.gov/strategicplanning/

National Institute of Environmental Health Sciences (NIEHS)

- Mission Statement: http://www.niehs.nih.gov/about/index.cfm
- Strategic Plan: http://www.niehs.nih.gov/about/strategicplan/index.cfm

National Institute on Aging (NIA)

- Mission Statement: http://www.nia.nih.gov/about/mission
- Strategic Plan: http://www.nia.nih.gov/about/living-long-well-21st-century-strategic-directions-research-aging

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: http://www.niams.nih.gov/About_Us/Mission_and_Purpose/long_range.asp

National Institute on Deafness and Other Communication Disorders (NIDCD)

- Mission Statement: http://www.nidcd.nih.gov/about/learn/pages/mission.aspx
- Strategic Plan: http://www.nidcd.nih.gov/about/plans/2012-2016/Pages/2012-2016-Strategic-Plan.aspx

National Institute of Mental Health (NIMH)

- Mission Statement: http://www.nimh.nih.gov/about/index.shtml
- Strategic Plan: http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml

National Institute on Drug Abuse (NIDA)

- Mission Statement: http://www.drugabuse.gov/about-nida
- Strategic Plan: http://www.drugabuse.gov/about-nida/2010-strategic-plan

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- Mission Statement: http://www.niaaa.nih.gov/about-niaaa
- Strategic Plan: http://www.niaaa.nih.gov/about-niaaa/our-work/strategic-plan

National Institute of Nursing Research (NINR)

- Mission Statement: http://www.ninr.nih.gov/AboutNINR/NINRMissionandStrategicPlan/
- Strategic Plan: http://www.ninr.nih.gov/AboutNINR/NINRMissionandStrategicPlan/

National Human Genome Research Institute (NHGRI)

- Mission Statement: http://www.genome.gov/27534788
- Strategic Plan: http://www.genome.gov/10001307

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

- Mission Statement: http://www.nibib.nih.gov/About/MissionHistory
- Strategic Plan: http://www.nibib.nih.gov/About/StrategicPlan

National Center for Research Resources (NCRR)[435]

- Mission Statement: http://www.ncats.nih.gov/about/about.html
- Strategic Plan:

National Center for Complementary and Alternative Medicine (NCCAM)

- Mission Statement: http://nccam.nih.gov/about/ataglance
- Strategic Plan: http://nccam.nih.gov/about/plans/2011

[435] 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).

National Institute on Minority Health and Health Disparities (NIMHD)

- Mission Statement: http://www.nimhd.nih.gov/about_ncmhd/mission.asp
- Strategic Plan: http://www.nimhd.nih.gov/about_ncmhd/index2.asp

John E. Fogarty International Center (FIC)

- Mission Statement: http://www.fic.nih.gov/About/Pages/mission-vision.aspx
- Strategic Plan: http://www.fic.nih.gov/About/Pages/Strategic-Plan.aspx

National Library of Medicine (NLM)

- Mission Statement: http://www.nlm.nih.gov/about/index.html
- Strategic Plan: http://www.nlm.nih.gov/pubs/plan/lrpdocs.html

NIH Clinical Center (CC)

- Mission Statement: http://clinicalcenter.nih.gov/about/welcome/mission.shtml
- Strategic Plan: http://www.cc.nih.gov/about/_pdf/2012CCOperatingPlan.pdf

Center for Information Technology (CIT)

- Mission Statement: http://www.nih.gov/about/almanac/organization/CIT.htm
- Strategic Plan: http://cit.nih.gov/NR/rdonlyres/54A93894-A76C-4742-A559-421738E78557/0/CITStrategicPlan2008Final.pdf

Center for Scientific Review (CSR)

- Mission Statement: http://public.csr.nih.gov/aboutcsr/Pages/default.aspx

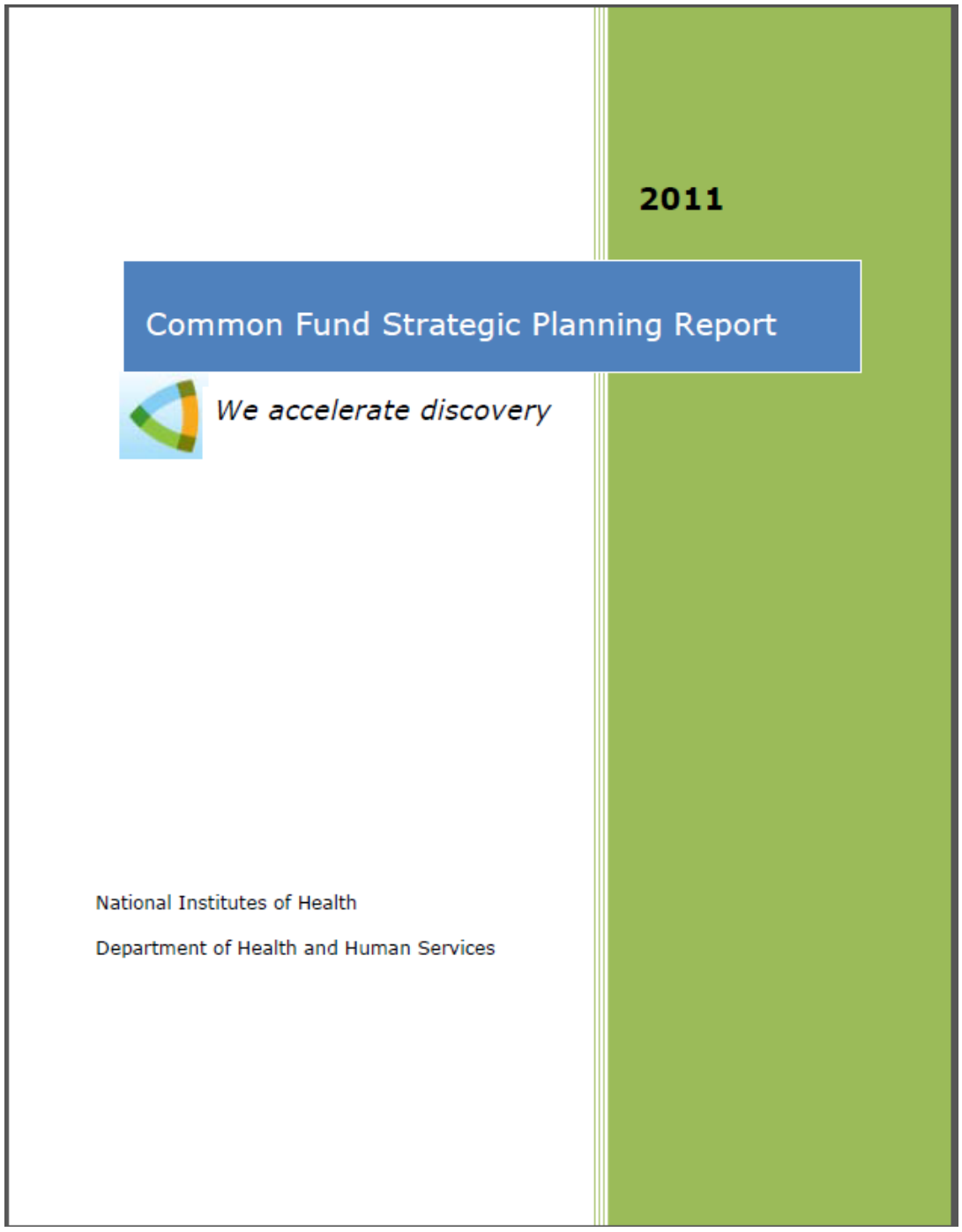
Office of the Director

- 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/oir/oir-staff.htm
- 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: http://www.nih.gov/icd/od/ocpl/mission.htm

- Office of Equal Opportunity and Diversity Management: http://oeodm.od.nih.gov/
- Office of Legislative Policy and Analysis: http://olpa.od.nih.gov/about/mission/default.asp
- Office of Ombudsman/Center for Cooperative Resolution: http://ombudsman.nih.gov/role.html
- NIH Ethics Office: http://ethics.od.nih.gov/overview.htm
- Office of the Chief Information Officer: http://ocio.od.nih.gov/about.html

Appendix C:
Common Fund Strategic Planning Report, 2011

This appendix provides the first 4 pages of the report. For the full report, please see http://commonfund.nih.gov/pdf/CF_Strat_Plng_Rept_2011_Final.pdf.



About the NIH Common Fund

The National Institutes of Health (NIH) Reform Act of 2006 established the Common Fund to support crosscutting, trans-NIH programs that attempt to remove shared obstacles to research progress or would otherwise benefit from strategic planning and coordination. Participation by at least two NIH Institutes or Centers (ICs) is required.

This broad mission has been refined in practice so that the Common Fund programs represent **strategic investments** in cross-cutting areas in which 5- to 10-year initiatives can have a transformative impact. Common Fund programs are therefore expected to address science that is unlikely to be funded by individual NIH ICs or other entities because of their scope or fundamental nature but which will catalyze research in many areas.

The Office of Strategic Coordination (OSC) within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) is responsible for managing and coordinating activities for the NIH Common Fund. Programs supported through the Common Fund are administered by the various NIH ICs.

Our Vision

Historically, Common Fund programs began in 2004 as initiatives under the NIH Roadmap for Medical Research. With the establishment of the Common Fund by the 2006 NIH Reform Act, these programs began to be referred to simply as "Common Fund Programs." The intent of these programs is to provide a strategic and nimble approach to address key *roadblocks* in biomedical research that impede basic scientific discovery and its translation into improved human health. In addition, these programs capitalize on *emerging opportunities* to catalyze the rate of progress across multiple biomedical fields.

Common Fund programs are expected to transform the way a broad spectrum of health research is conducted. Initiatives that comprise Common Fund programs are intended to be *catalytic* in nature, that is, stimulate further research through IC-funded mechanisms.

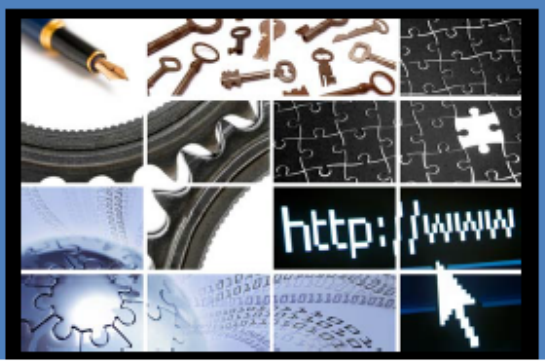
Criteria for Common Fund Programs:

Transformative: Programs have a high potential to affect, in a dramatic way, biomedical and/or behavioral research over the next decade

Synergistic: Multiple NIH Institutes and Centers work together to solve a shared challenge

Crosscutting: Programs address multiple Institute missions, and have relevance for multiple diseases and conditions

Broad Benefit: Concepts no other funding entity is likely or able to support, and research that benefits public health



Goal of Strategic Planning

Strategic planning is used to identify research areas that are not being supported by the ICs but which would enable and synergize with IC-funded research and would best be pursued via limited-term Common Fund investment. Input from NIH stakeholders and an analysis of the trans-NIH research portfolio are used to identify critical gaps or recent discoveries that have the potential to have a transformative impact.

The strategic planning process for the Common Fund varies from year to year to accommodate changing needs of the scientific community, the available level of research funds, emerging opportunities, and the desire to test and optimize new approaches. Although the specific process has varied slightly from year to year, core principles and activities underlie all the planning activities. These include:

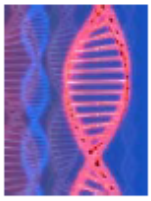
- Input is sought from people representing the perspectives of all ICs. This may take the form of input gathered directly from NIH staff and IC Directors or it may be provided through external scientists who represent trans-NIH research interests. The number of people whose input is sought is determined in part by the funds anticipated to be available for new programs. Regardless, Common Fund planning engages people from a wide range of disciplines—including individuals outside of biomedical research—and from individuals across a range of ages and experience levels.

- Input is gathered systematically and transparently rather than through *ad hoc* submission of individual unsolicited ideas. Although many possible Common Fund programs can be envisioned, only a small number can be supported. The process for soliciting ideas for new Common Fund programs must, therefore, be fair in its inclusion of representatives from across the NIH mission and must involve the review of many ideas together, so that competition among many ideas will result in the most compelling programs.

- The trans-NIH portfolio is assessed relative to the concepts that are identified by internal or external stakeholders. Portfolio review is an iterative process that helps in the selection of broad program areas as well as the development of specific initiatives within these broad areas.

- The leadership across NIH must be engaged early in the selection of new program areas to ensure that program development is focused on areas for which there is the greatest enthusiasm and broadest impact.

Common Fund programs do not focus on a specific disease, condition, or target population. They are intended to catalyze research across a broad spectrum of biomedical disciplines by supporting the development of catalytic tools, technologies, databases, models of research and funding, and other resources.



About the Strategic Plan

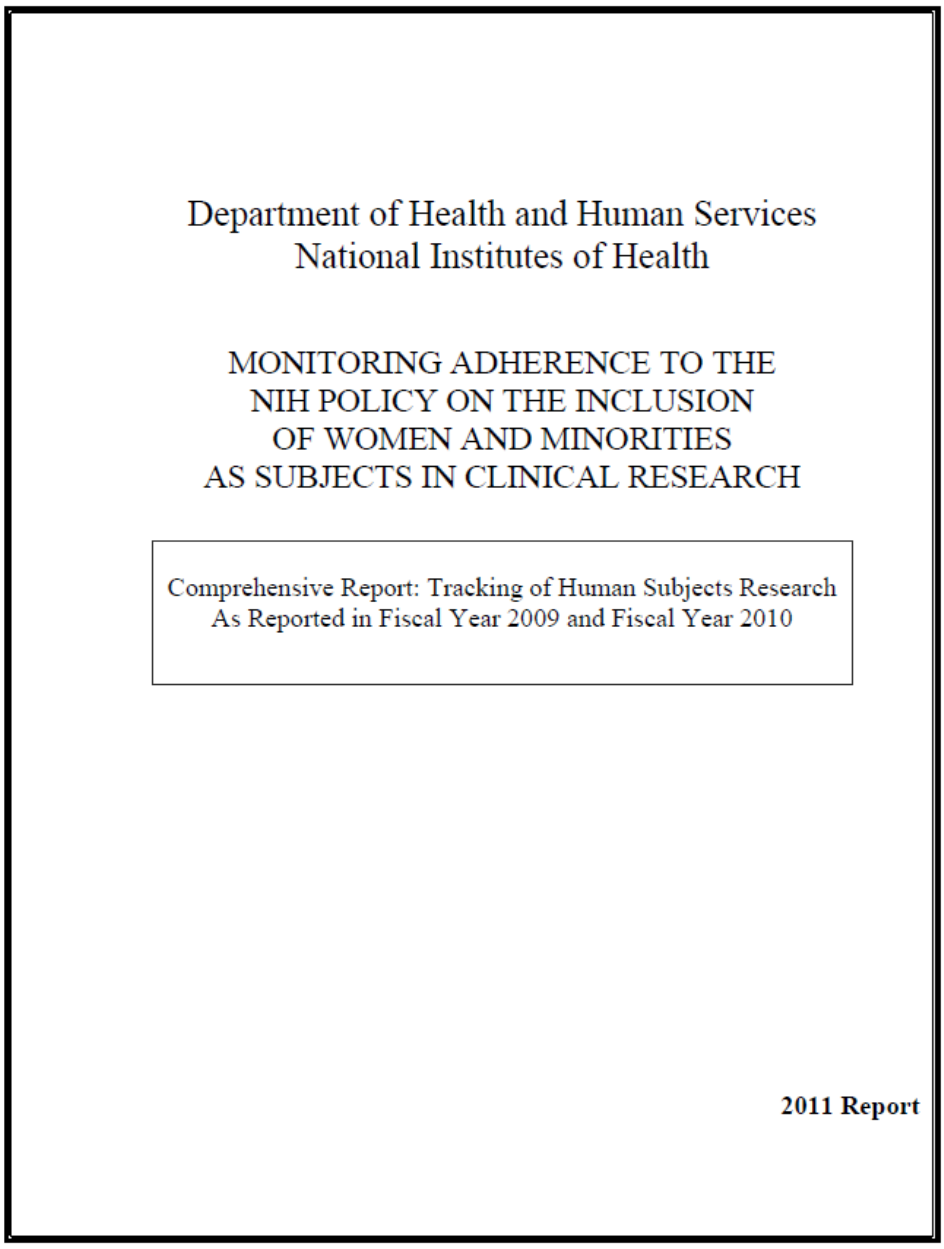
The Public Health Service Act requires the Director of the NIH to submit a report to Congress containing a strategic plan for funding research that, "...represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between two or more national research institutes or national centers, or would otherwise benefit from strategic coordination and planning" (42 U.S.C. §§ 282(b)(7)(A), 283(a)(3)).

This report describes:

- **Strategic planning activities for the Common Fund to date**
- **Status of Common Fund programs designed to meet needs articulated through strategic planning**
- **Plans for future strategic planning efforts for the Common Fund**

Appendix D:
Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

This appendix provides the first 8 pages of the report. 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 Human Subjects Research
As Reported in Fiscal Year 2009 and Fiscal Year 2010

2011 Report

Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

Historical Perspective

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by the National Institutes of Health (NIH) has its origins in the women's health movement. Following the issuance of the report of the Public Health Service Task Force on Women's Health in 1985[1], the NIH established a policy in 1986 for the inclusion of women in clinical research. This policy, which *urged* the inclusion of women, was first published in the NIH Guide to Grants and Contracts in 1987[2]. Later that year, minority and other scientists at the NIH recognized the need to address the inclusion of minority populations. Therefore, in a later 1987 version of the NIH guide, a policy *encouraging* the inclusion of minorities in clinical studies was first published.

In order to ensure that the policies for inclusion were firmly implemented by NIH, the Congress made what had previously been policy into Public Law, through a section in the NIH Revitalization Act of 1993 (PL 103-43)[3] entitled *Women and Minorities as Subjects in Clinical Research*. In 1994, NIH revised its inclusion policy to be in compliance with the statutory language. The Revitalization Act essentially reinforced the existing NIH policies, but with four major differences:

- that NIH ensure that women and minorities and their subpopulations be included in all clinical research;
- that women and minorities and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect;
- that cost is not allowed as an acceptable reason for excluding these groups; and,
- that NIH initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as participants in clinical studies.

Revised inclusion guidelines developed in response to this law were published in the *Federal Register*[4] in March 1994, and they became effective in September 1994. The result was that NIH could not and would not fund any grant, cooperative agreement or contract or support any intramural project to be conducted or funded in Fiscal Year 1995 and thereafter which did not comply with this policy.

Strategies to ensure uniform implementation and adherence to the revised guidelines across the NIH included NIH –wide training of staff and Institutonal Review Board chairs in 1994. An NIH Tracking and Inclusion Committee was established made up of representatives of the directors of each of the Institutes and Centers (ICs). This trans-NIH committee, convened by the Office of Research on Women's Health (ORWH) and co-chaired with a senior IC official, met on a regular basis, focusing on consistent and widespread adherence to the NIH guidelines by all the ICs. Working in collaboration with the Office of Extramural Research (OER), the Office of Intramural Research (OIR), and other components of NIH, ORWH coordinated the development of data collection and reporting methodologies to ensure uniform standards and definitions in the reporting of data on women and minority participants in NIH-funded clinical research.

In addition, a variety of outreach activities were initiated to explain the revised policy to the scientific research community and to clear up common misunderstandings about the new requirements. Training was especially important in light of 1990 General Accounting Office (GAO) findings that NIH's initial

policy on inclusion was inconsistently applied and had not been well communicated or understood within NIH or in the research community.

GAO Report, May 2000: Recommendations and Actions Taken

Following a Congressional request for an assessment of NIH progress in implementing the1994 guidelines on including women in clinical research, the GAO issued another report in May, 2000, entitled *Women's Health - NIH Has Increased Its Efforts to Include Women in Research.*[5] It concluded that in the past decade, NIH had made significant progress in implementing a strengthened policy on including women in clinical research.

The GAO report also included two specific recommendations to the Director of NIH:

- that the requirement be implemented that Phase III clinical trials be designed and carried out to allow for the valid analysis of differences between women and men and communicate this requirement to applicants as well as requiring peer review groups to determine whether each proposed Phase III clinical trial is required to have such a study design, and that summary statements document the decision of the initial reviewers; and

- that NIH staff members who transmit data to the inclusion tracking data system receive ongoing training on the requirements and purpose of the system.

Immediately following the release of this report, a *NIH Subcommittee Reviewing Inclusion Issues* was formed, consisting of representatives from several ICs, ORWH, OER, and OIR, to reexamine NIH's system for tracking data on the inclusion of women and minorities in clinical research, recommend any necessary changes to improve its accuracy and performance, and reiterate the NIH policy. Several actions resulted to clarify the requirement for inclusion of women and minority groups, where scientifically appropriate, in NIH-funded clinical research. In addition, NIH-defined Phase III clinical trials are required to include plans for analysis of sex/gender and/or racial/ethnic differences. Significant actions in 2001 included:

- **Updating the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research**[6] and posting it on the ORWH home page http://orwh.od.nih.gov/inclusion.html and NIH web page, *Inclusion of Women and Minorities Policy Implementation* at: http://grants.nih.gov/grants/funding/women_min/women_min.htm

- **Developing a new term and condition of award** statement for awards made after October 1, 2000 that have NIH-defined Phase III clinical trials.

- **Incorporating language in NIH solicitations for grant applications and contract proposals to clarify the submission requirement for NIH-defined Phase III clinical trials**, a description of plans for sex/gender and/or race/ethnicity analysis including subgroups, if applicable, and reporting enrollment annually and results of analyses, as appropriate.

- **Guidelines and instructions for reviewers and Scientific Review Officers (SROs) were developed** to emphasize and clarify the need to review research proposals that are classified as NIH-defined Phase III clinical trials for both inclusion requirements and issues related to analyses by sex/gender and/or race/ethnicity. Instructions were developed for the proper documentation to include in summary statements to address adherence to these policies.

Training to ensure compliance with this policy was provided to NIH program and review officials, grants and contracts management staff, and current and prospective research investigators. Several initiatives were implemented for review, grants management and program staff since 2000, including specific topics addressing revisions to the NIH Inclusion policy, a grants policy update and Scientific Review Officer (SRO) orientation on specific issues related to review meetings and proceedings.

Format Changes for Reporting Race and Ethnicity Data as of FY2002

Beginning in FY2002, NIH changed how data are reported based on the 1997 Office of Management and Budget (OMB) revisions to the 1977 Directive 15 "Race and Ethnic Standards for Federal Statistics and Administrative Reporting," which provided minimum standards for maintaining, collecting and reporting data on race and ethnicity. In October 1997, OMB published "Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity; and their implementation involved a number of changes, including collecting and reporting information on race and ethnicity separately, whereas the 1977 OMB standards used a combined race and ethnicity format. NIH aggregate population data tables describe data using both the 1997 and 1977 OMB standards for reporting data on race and ethnicity. Since 2002, the number of studies reporting data using the 1997 format (NEW FORM) has steadily increased, whereas the number of studies using the 1977 format (OLD FORM) has steadily decreased as the studies funded prior to FY2002 are completed.

The 1997 OMB reporting format (NEW FORM) and standards do not easily allow direct comparison of ethnic and racial data with similar data collected under the 1977 OMB reporting format (OLD FORM) and standards because the categories and methods for collecting the data are fundamentally different. Changes in the standardization of definitions and business rules across NIH for improving the data entered in the population tracking system are reflected in data reported beginning in FY2002. While implementation of these changes will improve the consistency and comparability for future reporting, comparisons with data originating prior to FY 2002 data are difficult although trends can be approximated.

As demonstrated below, the primary differences are: (1) the Hispanic population is considered an ethnic category and reported separately from racial data; (2) there are separate racial categories for Asian population data as distinct from Hawaiian and Pacific Islander population data; and 3) respondents are given the option of selecting more than one race.

Race and ethnicity data from the OLD and NEW Forms are combined differently as described below for purposes of reporting on the minority population enrolled in NIH clinical research:

- The OLD FORM uses the 1977 OMB combined Race and Ethnicity Format, which has mutually exclusive categories, and allows Hispanics to be reported as either "Hispanic, Not White" or "White".

- The NEW FORM uses the 1997 OMB Race and Ethnicity Categories, with separate reporting for Ethnicity (Hispanic or Latino; Not Hispanic or Latino) and Race (Part A); in this format, an individual is classified both by Ethnic Category and by Race Category. Part B of the NEW FORM therefore provides a distribution of only "Hispanics or Latinos" by the five main Race categories. Since minority categories are defined to include both "Hispanic or Latino ethnicity" and non-white racial categories when providing summary totals of minorities, it is necessary to add White Hispanics" and "Unknown/Other Hispanics" based on their ethnicity to the non-white racial categories.

- Hispanics are defined by country of origin, and may be identified as belonging to any one race, or more than one racial category.

Targeted/Planned Enrollment: Comparison of Old (1977) and New (1997) Forms

I. Old Form (1977 OMB Race/Ethnicity Categories)

Race/Ethnicity Category	Inclusion in Minority Total
American Indian/Alaska Native	X
Asian/Pacific Islander	X
Black or African American	X
Hispanic, Not White	X
White	
Unknown/Other	

II. New Form (1997 OMB Race./Ethnicity Categories)

Part A. Total Enrollment Report

Racial / Ethnic Categories	Racial or Ethnic Category	Inclusion in Minority Total
American Indian/Alaska Native	Racial	X
Asian	Racial	X
Black or African American	Racial	X
Hawaiian/Pacific Islander	Racial	X
White	Racial	
More Than One Race	Racial	X
Unknown/Other	Racial	
Racial Categories: Total of all Subjects	**Racial Total***	
Hispanic or Latino	Ethnic**	
Not Hispanic or Latino	Ethnic	
Unknown (ethnicity not reported)	Ethnic	
Ethnic Categories: Total of All Subjects	**Ethnic Total***	

Part B: Hispanic Enrollment Report

Racial / Ethnic Categories	Racial or Ethnic Category	Inclusion in Minority Total
American Indian/Alaska Native	Ethnic	
Asian	Ethnic	
Black or African American	Ethnic	
Hawaiian/Pacific Islander	Ethnic	
White (Hispanic)	Ethnic	X
More Than One Race	Ethnic	
Unknown/Other (Hispanic)	Ethnic	X
Racial Categories: Total of Hispanics or Latinos	Ethnic Total**	

*** The "Ethnic Categories: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects"**
**** The "Hispanic or Latino"(Part A) must be equal to "Racial Categories: Total of Hispanics or Latinos"(Part B).**

Continuing Implementation and Monitoring Activities

The PHS 398 grant application was significantly revised to provide additional instructions concerning the Women and Minorities Inclusion Policy and the new enrollment form became mandatory as of May 10, 2005. These PHS 398 instructions are also included in the federal application form SF-424 (R&R) for NIH grants using the federal Grants.gov system (http://era.nih.gov/ElectronicReceipt/) including two significant changes in definitions. First, NIH requires use of a revised definition of clinical research that was reported in the 1997 Report of the NIH Director's Panel on Clinical Research and adopted by NIH. Second, NIH adopted the 1997 revisions to OMB Directive 15, "Race and Ethnic Standards for Federal Statistics and Administrative Reporting", and required the revised categories to be used when reporting race and ethnic data (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html). In addition, NIH policy reemphasized that that NIH-defined Phase III clinical trials must be designed and conducted in a manner to allow for a valid analysis of whether the interventions being studied affect women or members of minority groups differently than other subjects.

In FY 2007, two training sessions were developed for NIH staff involved in the management or review of clinical research studies. Approximately 300 NIH staff members attended each session in person, and additional staff participated in the training via webcast.

Communication and Outreach Efforts to the Scientific Community

NIH staff members provide outreach to the scientific community to help increase understanding of any revised inclusion policies. These training and outreach efforts improve understanding of the sex/gender and minority inclusion policy and assist investigators and NIH intramural research staff to appropriately address these issues throughout the research grant and contract process. Investigators are instructed to address women and minority inclusion issues in the development of their applications and proposals for clinical research.

Reference documents such as the *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research* (http://orwh.od.nih.gov/inclusion/outreach.pdf) and the *Frequently Asked Questions (FAQs) for the Inclusion , Recruitment and Retention of Women and Minority Subjects in Clinical Research* (http://orwh.od.nih.gov/inclusion/outreachFAQ.pdf) have been published and distributed for investigators and NIH staff. These publications discuss the elements of recruitment and retention, the NIH inclusion policy, current OMB requirements for reporting race and ethnicity data, and information for application submission, peer review, and funding. Both the Outreach Notebook and the FAQs are posted on the ORWH website http://orwh.od.nih.gov as well as on the NIH website for the inclusion of women and minorities policy implementation at: http://grants1.nih.gov/grants/funding/women_min/women_min.htm. The revised Outreach Notebook and FAQs continue to be available to the research community to further explore the inclusion policy and its intent. Additionally, a slide show is available electronically and in hard copy, entitled "Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!" The slide show was developed for NIH staff to assist them in working with the extramural community.

Monitoring Compliance: Extramural and Intramural Population Data Analysis

Inclusion enrollment data from each NIH Institute and Center are presented in this report in aggregate data tables, providing documentation of the monitoring of inclusion with some degree of analysis of data. Caution should be used in interpreting these figures. Conclusions that can be reasonably drawn from the data are provided.

When assessing inclusion data, enrollment figures should not be directly compared to the national census figures. The goal of the NIH policy is to conduct biomedical and behavioral research in such a manner that the scientific knowledge acquired will be generalizable to the entire population of the United States, and not to satisfy any proportional target based upon census data. The number of women, men and/or representatives of racial/ethnic subpopulations included in a particular study depends upon the scientific question addressed in the study and the prevalence among women, men and/or racial/ethnic subpopulations of the disease, disorder, or condition under investigation.

Scientific Review Groups are instructed to focus on scientific considerations when assessing the planned enrollment described in a NIH grant application for a proposed study. The Scientific Review Group (SRG) evaluates the inclusion plan and finds it unacceptable if it: 1) fails to provide sufficient information about target enrollment; 2) does not adequately justify limited or lack of inclusion of women or minorities; or 3) does not realistically address recruitment and retention. For NIH-defined Phase III clinical trials, the SRG also evaluates the description of plans to conduct analyses, as appropriate, to address differences in the intervention effect by sex/gender and/or racial/ethnic groups. Applications with unacceptable inclusion plans cannot be funded until NIH staff members are assured that revised inclusion plans meet the inclusion policy requirements. Research awards covered by this policy require the grantee to report annually on enrollment of women and men, and on the race and ethnicity of research participants so that enrollment can be monitored.

NIH has monitored aggregate inclusion data for study populations through the evolving NIH automated tracking system since FY1994 and monitoring compliance with the NIH Inclusion policy is well established in all IC's. In May 2002, the NIH successfully deployed a population tracking system for monitoring inclusion data that was designed to provide easier entry of investigator-reported enrollment data and project monitoring for NIH staff. An *eRA Population Tracking User Group* consisting of representatives from several ICs provides continuous feedback related to procedures to monitor compliance.

DEFINITIONS:

Clinical Research as defined by the 1997 Report of the NIH Director's Panel on Clinical Research, (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; (2) Epidemiologic and behavioral studies; and (3) Outcomes research and health services research.

NIH-Defined Phase III Clinical Study
For the purpose of these guidelines, an NIH-defined "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence

leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Valid Analysis
The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,
- unbiased evaluation of the outcome(s) of study participants, and
- use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

Significant Difference
For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

Domestic organization
A public (including a State or other governmental agency) or private non-profit or for-profit organization that is located in the United States or its territories, is subject to U.S. laws, and assumes legal and financial accountability for awarded funds and for the performance of the grant-supported activities

Foreign institution
An organization located in a country other than the United States and its territories that is subject to the laws of that country, regardless of the citizenship of the proposed PI.

CONCLUSION AND CURRENT STATUS

NIH staff continue to monitor, document, and work with grantees and contractors to ensure compliance with the inclusion policy. Program officers/staff provide technical assistance to investigators as they develop their applications and proposals throughout the application process. Review officers introduce and discuss with reviewers the Guidelines/Instructions for reviewing the Inclusion of Women and Minorities in Clinical Research as well as the instructions and requirements for designing Phase III Clinical Trials in order that valid analyses can be conducted for sex/gender and ethnic/racial differences. At the time of award and submission of progress reports, program officials monitor and verify that inclusion policy requirements are met. When new and competing continuation applications that are selected for payment are deficient in meeting policy requirements, grants management staff and program officials are required to withhold funding until the principal investigator has satisfactorily addressed the policy requirements.

References

1. Report of the Public Health Task Force on Women's Health: US Public Health Service, 1985. Jan-Feb; 100(1):73-106.

2. NIH Guide to Grants and Contracts, Vol. 16, No. 3, Pg 2, January 23, 1987.

3. Public Law 103-43. National Institutes of Health Revitalization Act of 1993. 42 USC 289 (a)(1).

4. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508-14513 (1994).

5. *Women's Health: NIH Has Increased Its Efforts to Include Women in Research* (GAO/HEHS-00-96, May, 2000).

6. NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, NIH Guide for Grants and Contracts, Amended 2001.

For additional information on the implementation of the inclusion policy, please visit:

NIH Office of Extramural Research Inclusion of Women and Minorities Policy Implementation Website: HYPERLINK "http://grants.nih.gov/grants/funding/women_min/women_min.htm" http://grants.nih.gov/grants/funding/women_min/women_min.htm

Revitalization Act of 1993, 42 USC 289 (a)(1): HYPERLINK "http://grants.nih.gov/grants/guide/notice-files/not94-100.html" http://grants.nih.gov/grants/guide/notice-files/not94-100.html

NIH Policy on Reporting Racial and Ethnicity Data: Subjects in Clinical Research, NIH Guide for Grants and Contracts Web page: HYPERLINK "http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html" http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html

Office of Research on Women's Health Website: HYPERLINK "http://orwh.od.nih.gov/inclusion.html" http://orwh.od.nih.gov/inclusion.html

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[436]

Field of Study	FY 2009	FY 2010
Life Sciences	**2,431**	**2,466**
Biological/Biomedical Sciences	**2,214**	**2,214**
Anatomy	3	1
Bacteriology	9	11
Biochemistry	203	192
Bioinformatics	37	26
Biology/Biological Sciences, General	43	50
Biology/Biomedical Sciences, Other	12	13
Biomedical Sciences	82	74
Biometrics & Biostatistics	22	31
Biophysics	57	69
Biotechnology	2	5
Botany/Plant Biology	6	6
Cancer Biology	82	105
Cell/Cellular Biology and Histology	125	122
Computational Biology	0	18
Developmental Biology/Embryology	56	61
Ecology	4	5
Endocrinology	8	4
Entomology	2	1
Evolutionary Biology	20	21
Genetics, Human & Animal	125	130
Immunology	190	205
Microbiology	185	132
Molecular Biology	199	184
Neuroscience	447	413
Nutritional Sciences	18	25

[436] Source: Data drawn from NIH Trainee and Fellow File, IMPAC II, and the Doctorate Records File on 6/5/2012.

Field of Study	FY 2009	FY 2010
Parasitology	6	15
Pathology, Human & Animal	30	26
Pharmacology, Human & Animal	138	98
Physiology, Human & Animal	48	72
Plant Genetics	6	6
Plant Pathology/Phytopathology	0	1
Structural Biology	0	15
Toxicology	44	28
Virology	0	48
Zoology	5	1
Health Sciences	**213**	**250**
Environmental Health	3	6
Environmental Toxicology	6	0
Epidemiology	52	91
Gerontology	0	1
Health Sciences, General	5	0
Health Sciences, Other	7	8
Health Systems/Service Administration	3	2
Kinesiology/Exercise Sciences	4	5
Medicinal/Pharmaceutical Sciences	23	21
Nursing Science	57	50
Oral Biology/Oral Pathology	0	3
Public Health	35	42
Rehabilitation/Therapeutic Services	5	4
Speech-Language Pathology & Audiology	10	10
Veterinary Sciences	3	7
Agricultural Sciences/Natural Resources	**4**	**2**
Agricultural and Horticultural Plant Breeding	0	0
Agricultural Economics	0	0
Agricultural Science, Other	0	0
Environmental Science	3	1
Fishing and Fisheries Sciences/Management	0	0
Food Sciences and Technology, Other	0	1
Horticulture Science	0	0
Plant Pathology/Phytopathology	1	0
Plant Sciences, Other	0	0

Field of Study	FY 2009	FY 2010
Soil Chemistry/Microbiology	0	0
Soil Sciences, Other	0	0
Social Sciences	**291**	**303**
Psychology	**227**	**240**
Clinical Psychology	91	93
Cognitive & Psycholinguistics	34	28
Comparative Psychology	0	0
Counseling	2	2
Developmental & Child Psychology	23	28
Educational Psychology	0	1
Experimental Psychology	9	9
Family Psychology	1	0
Human Development & Family Studies	11	8
Industrial & Organizational Psychology	0	1
Personality Psychology	4	3
Physiological/Psychobiology	18	27
Psychology, General	4	10
Psychology, Other	7	6
Psychometrics & Quantitative	3	3
School Psychology	1	0
Social Psychology	19	21
Social Sciences	**64**	**63**
Anthropology	7	2
Criminal Justice and Corrections	2	0
Criminology	0	0
Demography/Population Studies	3	4
Economics	12	11
Geography	1	0
Linguistics	2	2
Political Science and Government	1	0
Public Policy Analysis	3	6
Social Sciences, General	0	1
Social Sciences, Other	1	3
Sociology	32	34
Statistics	0	0
Physical Sciences	**156**	**139**

Field of Study	FY 2009	FY 2010
Chemistry	**93**	**83**
Analytical Chemistry	11	19
Chemistry, General	12	7
Chemistry, Other	16	17
Inorganic Chemistry	7	10
Organic Chemistry	34	20
Medicinal/Pharmaceutical Chemistry	0	0
Physical Chemistry	10	6
Polymer Chemistry	3	2
Theoretical Chemistry	0	2
Computer Sciences	**13**	**5**
Computer Science	8	2
Computer & Information Sciences, Other	4	3
Information Science & Systems	1	0
Mathematics	**19**	**22**
Analysis and Functional Analysis	1	1
Applied Mathematics	4	6
Computing Theory and Practice	0	0
Geometry/Geometric Analysis	0	0
Mathematics/Statistics, Other	1	3
Statistics	13	12
Topology/Foundations	0	0
Ocean/Marine Sciences	**1**	**1**
Oceanography, Chemical and Physical	0	1
Marine Sciences	1	0
Physics	**29**	**28**
Acoustics	0	0
Applied Physics	4	1
Atomic/Molecular/Chemical Physics	0	1
Biophysics	13	10
Condensed Matter/Low Temperature Physics	0	1
Medical Physics/Radiological Science	0	9
Nuclear Physics	1	0
Optics/Phototonics	3	1
Particle (Elementary) Physics	0	0
Physics, General	4	2

Field of Study	FY 2009	FY 2010
Physics, Other	4	3
Plasma/Fusion Physics	0	1
Polymer Physics	0	0
Engineering	**198**	**189**
Aerospace, Aeronautical and Astronautical	1	0
Bioengineering and Biomedical	146	138
Chemical	25	26
Civil	1	0
Computer	0	0
Electrical, Electronics and Communications	9	14
Engineering Mechanics	0	1
Engineering, Other	2	1
Environmental Health Engineering	0	1
Industrial and Manufacturing	0	0
Materials Science	6	2
Mechanical	6	5
Nuclear	0	0
Ocean	1	0
Operations Research	1	0
Polymer and Plastics	1	0
Systems	0	1
Education	**11**	**20**
Humanities	**3**	**5**
Other Fields	**29**	**18**
TOTAL	**3,119**	**3,140**

Demographic Characteristics of NRSA Participants[437]

Characteristic	FY 2009	FY 2010	FY 2011
Gender			
Female	52.5%	52.3%	52.6%
Male	45.3%	44.8%	45.2%
Unknown	1.4%	1.6%	0.2%
Withheld	0.8%	1.3%	2.0%
Race			
White	64.8%	64.5%	65.3%
Asian	14.9%	14.6%	14.0%
African American	7.2%	7.2%	7.1%
Native American	0.8%	0.7%	0.6%
Native Hawaiian/Pacific Islander	0.4%	0.3%	0.3%
Multiple Races (including more than 1 race)	1.2%	1.8%	2.9%
Unknown	5.6%	5.2%	3.4%
Withheld	5.2%	5.7%	6.5%
Ethnicity			
Hispanic	7.6%	7.8%	8.8%
Non-Hispanic	80.6%	80.3%	80.9%
Unknown	9.9%	9.3%	6.7%
Withheld	2.0%	2.7%	3.5%

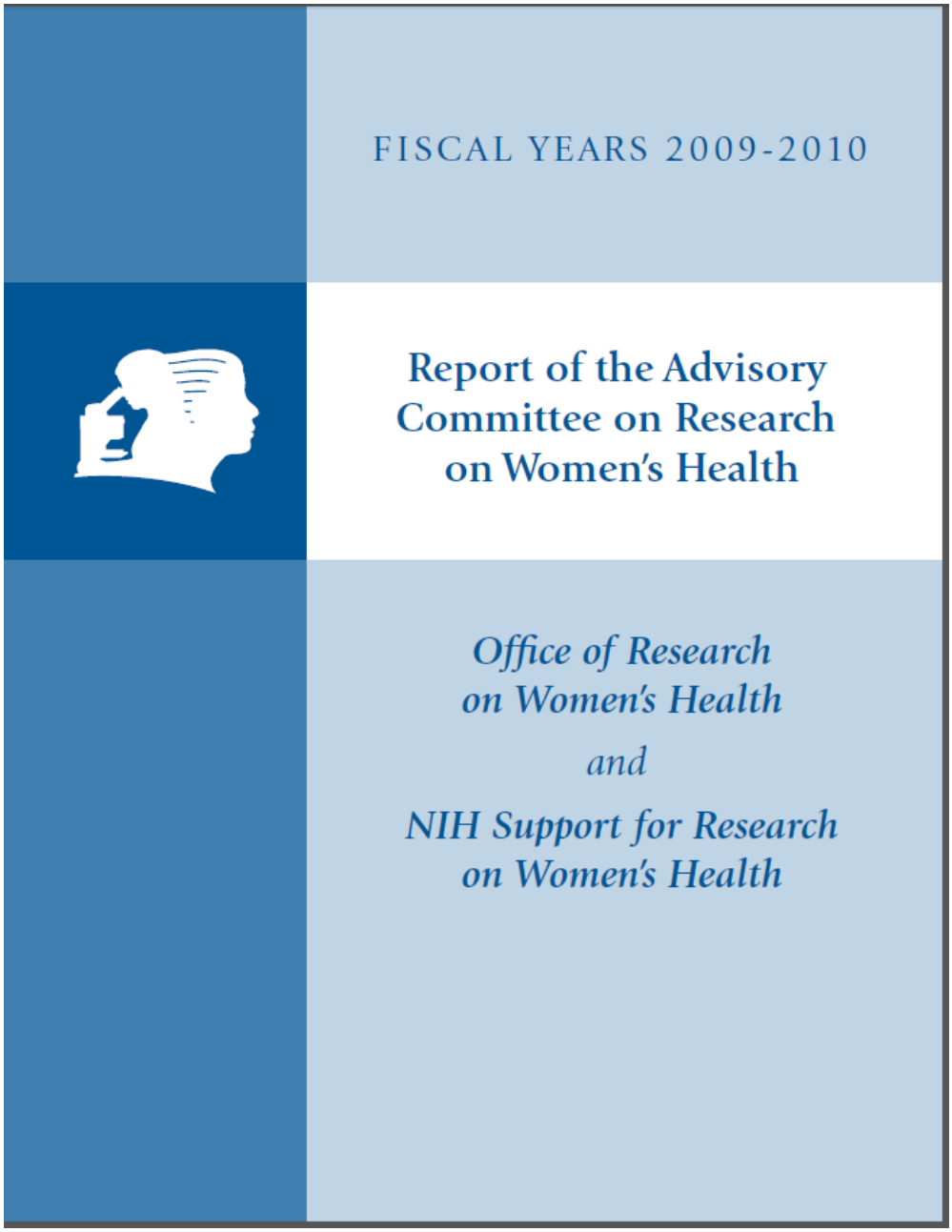
[437] Source: Data drawn from IMPAC II Current Files for Trainees & Pub files for Fellowships as of 6/4/2012 and is subject to change. For individuals whose Race or Ethnicity was Unknown or Withheld, IMPAC II data were supplemented with information from the Doctorate Records File.

Successfully Completed Residency and Subspecialty Training By Academic Year

NIH Clinical Center Program Specialty	Successfully Completed	
	2009/2010	2010/2011
Allergy and Immunology	3	1
Medical Genetics	4	1
Medical Biochemical Genetics	2	0
Critical Care Medicine	3	4
Endocrinology, Diabetes, and Metabolism	5	5
Hematology	2	4
Infectious Disease	5	2
Oncology	4	12
Rheumatology	3	4
Pathology-Anatomic and Clinical	3	4
Blood Banking/Transfusion Medicine	2	2
Cytopathology	1	1
Hematology (Pathology)	2	3
Pediatric Endocrinology	1	2
Psychiatry	1	2
Vascular Neurology	2	2
Hospice and Palliative Medicine	1	4
Neurological Surgery (new program)	0	0
Total	44	53

Appendix F:
Report of the Advisory Committee on Research on Women's Health

This appendix provides the introduction of the report. For the full report, please see http://orwh.od.nih.gov/about/acrwh/pdf/Report-of-the-ACRWH-FY-2009-2010.pdf.



Introduction

This report of the Advisory Committee on Research on Women's Health (ACRWH) for fiscal years (FY) 2009–2010 provides a summary of the accomplishments of the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) to address women's health over the past 2 years. It documents the expansive growth of women's health and sex differences research along with many other significant programs and activities across the NIH. As requested in the NIH Revitalization Act of 1993, the ACRWH, a chartered group composed of non-Federal experts, submits a report to the NIH Director every 2 years describing its findings related to the mandates for ORWH and NIH support of women's health research. This document fulfills that directive.

During FY 2009 and FY 2010, the time period addressed in this report, a number of milestones were reached. In September 2010, the ORWH celebrated the 20th anniversary of its historic establishment in 1990 as the first office within the U.S. Department of Health and Human Services to focus specifically on women's health. The anniversary celebration brought together women and men involved in women's health at the NIH as well as in the extramural community as researchers, health care providers, advocates, mentors, educators, policymakers, legislators, and other interested and dedicated individuals.

ORWH marked its first 20 years with a scientific symposium that recounted the many women's health research advances of the last two decades. At this time, ORWH also introduced a new strategic plan and research agenda for the NIH, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research* (NIH Publication No. 10-7606), which provides a plan for future women's and sex differences health research and career advancement in biomedical sciences for the coming decade. This new strategic plan, described in some detail in this report on page 9, represents the third multiyear effort by the ORWH to consult various women's health constituencies to determine the direction in which women's health research should proceed and, thus, determine priorities for new research and other funding initiatives. ORWH and other components of the NIH have used each of the previous strategic plans to move research opportunities forward and to explore the continuing gaps in knowledge about women's health and related issues.

Much progress in women's health research has been accomplished, including the following:

- A better understanding of what constitutes women's health and why
- Expanded concepts that embrace women's health across the lifespan rather than focusing exclusively on the reproductive system
- More exacting scientific endeavors using the most current diagnostic or investigative tools and skills

The new NIH strategic plan will also provide the impetus for even more advanced and redefined pathways for research initiatives in the future. ORWH has already begun to implement these new research priorities with enthusiastic trans-NIH participation. Vital to this effort is the participation and leadership of the Coordinating Committee on Research on Women's Health (CCRWH), composed of IC and Program Office directors or their representatives. Therefore, it is expected that exciting and important advances in women's health and sex differences research and career development programs can be anticipated during the years to come.

Several other milestones that should be noted with the submission of this report require personal comments. The ORWH was designed and established in 1990 by Dr. Ruth Kirschstein (at that time, the only woman director of an NIH Institute and cochair of the Public Health Service Committee on Women's Health Issues) under the leadership of Dr. William Raub, then Acting

Director of NIH. Dr. Kirschstein served as the Acting Director of ORWH until I came to the NIH in the fall of 1991 as the first full-time Director of ORWH under the leadership, support, and encouragement of Dr. Bernadine Healy, then Director of NIH, and the only woman to hold that position in the history of the NIH.

There is no doubt that the operational processes and premises for the ORWH, as established by Dr. Kirschstein, have continued to serve the ORWH and the NIH well over the past 20 years. And, there should also be no doubt that the extensive array of NIH women's health programs was possible only because of the vision that Dr. Healy had for the role that NIH should and could have in leading efforts to increase the scientific foundation for women's health care. So to both of these women leaders I, and the ORWH owe gratitude for the lasting impact their visions and their actions will have on the future of women and the science of women's health. The death of both of these trailblazers during these recent years must remind all of us to continue to build on their vision and their efforts as we move forward under the new research agenda for the coming decade and beyond.

And, finally, this report marks the end of my tenure as Director of the Office of Research on Women's Health and Associate Director of NIH for Research on Women's Health. The past nearly 20 years have, for me, been among the most personally fulfilling experiences, and I am grateful for having been given the opportunity to lead this effort for the NIH.

I have had the benefit of tremendous support and assistance from a wonderful and dedicated ORWH staff; wise and beneficial advice and collaboration from so many members of the NIH community; and exciting and stimulating encouragement from and partnerships with individuals, organizations, and legislators—especially members of the Congressional Caucus on Women's Issues, the actions of which led to the development of this Office, and whose continued interest and support have helped to sustain it. I have witnessed the growth of the ORWH, its dimensions of influence and programs, and its collaborative role in invoking science-based initiatives to augment the scientific foundation for women's health. The current state of NIH women's health research and programs constitutes this biennial report.

Organization of the FY 2009–2010 Biennial Report of the ACRWH

This FY 2009–2010 biennial report of the ACRWH bears witness to the phenomenal growth in women's health research and related programs that has occurred since the formation of the Office in 1990. It reflects major FY 2009–2010 ORWH research programs, initiatives, and activities, as well as highlights that were reported through the CCRWH from the NIH ICs and Program Offices. This report is not a comprehensive listing of all NIH research on women's health, which would necessarily be encyclopedic; the report does serve, however, to summarize, under a single cover, examples of the wealth of NIH advances in women's health research. This biennial report also provides information on and analyses of support for women's health research and related activities. The budget figures for NIH expenditures on women's health research and programs during FY 2009–2010 are included in this report, but are provided in a slightly different format because of the American Recovery and Reinvestment Act of 2009 (ARRA) funding during these years, which is accounted for separately.

This biennial report is divided into two major parts: part 1 presents ORWH programs and part 2 provides individual reports on women's health research from the NIH ICs and Program Offices. Information about ORWH programs in part 1 is organized into the following seven sections:

I. ORWH Research
II. ORWH Interdisciplinary Research and Career Development Programs
III. ORWH Biomedical Career Development Activities
IV. ORWH Research Dissemination and Outreach

V. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

VI. NIH Budget for Women's Health Research

VII. Committee Members, FY 2009–2010

Section I provides a table of ORWH-funded projects grouped by diseases and conditions, examples of special ORWH research initiatives, and highlights of scientific workshops and conferences. The voluminous research that has occurred because of ORWH support or with ORWH cofunding is well documented in this section, representing an investment in basic and clinical scientific investigations into ongoing gaps in knowledge about normal aspects of women's health; disease processes that may be unique to women, or affect both men and women with potential differences yet to be defined; and newly recognized conditions that may affect the wellness or mortality of women across their lifespan.

The previous strategic plan under which the ORWH was operating during this time period, *The Agenda for Research on Women's Health for the 21st Century*, recognized that women's health research is an inherently broad interdisciplinary endeavor, encompassing a full range of scientific activities. Since 1999, ORWH has been working to provide individual and institutional support for interdisciplinary research and career development. As the 20th anniversary of the office was celebrated, it became apparent that the ORWH-initiated interdisciplinary initiatives have evolved into the signature programs of new and exciting efforts in women's health research that are changing institutional approaches; these efforts and programs are described in detail in section II.

Section III provides information on a number of other programs through which ORWH works to promote women's biomedical career development and the development of careers in research on women's health and sex/gender factors. The ORWH-initiated, trans-NIH Reentry into Biomedical and Behavioral Careers Research Supplement Program is also described, representing an ORWH pilot initiative that now, as a trans-NIH program of the ICs, continues to be important for sustaining careers in research for those with family responsibilities that have interrupted their commitment to careers as scientists. This section also describes the activities of the NIH Director's Working Group on Women in Biomedical Careers to provide a comprehensive, action-oriented NIH response to challenges to Federal agencies posed in the 2007 National Academies report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*.

Section IV on research dissemination and outreach provides information on new ORWH Internet-based health information initiatives, including an ongoing collaborative effort with the NIH National Library of Medicine as part of its online resources for information on women's health research; a Web-based series of courses cosponsored with the Food and Drug Administration on *The Science of Sex and Gender in Human Health*; a multimedia approach to communicate advances being made from past and current women's health research; and other efforts to ensure that information generated from the NIH investment in research on women's health informs future research efforts and improves women's health and health care. Additional ORWH research dissemination and outreach activities, including the Women's Health Seminar Series, are also detailed in section IV.

Section V details NIH efforts to monitor the inclusion of women and minorities in NIH-funded clinical research, including aggregate data on the numbers of women, men, and minorities who participated as volunteers in NIH clinical research.

Section VI provides information on NIH expenditures on women's health research, including a breakdown of expenditures by disease category and other major categories of interest.

Part 2 of the biennial report is composed of individual reports from 19 NIH Institutes, 3 Centers, and 3 Program Offices located within the NIH Office of the Director. These IC and Office reports summarize their major initiatives and activities and provide highlights of the research

each has funded related to women's health and sex differences research, consistent with their specific missions. This information is presented as submitted by the ICs, most often by their CCRWH representatives, and is impressive as well as fascinating in its scope and dimensions.

You are invited to read this in-depth report to become acquainted with the tremendous advances in women's health and sex differences research that have taken place during this 2-year period and to appreciate the promise for even greater advances in the future; not just for women's health, but also for men's health through enhanced attention to sex differences research; and for careers in women's health research for both men and women.

I am encouraged, as I entrust the leadership of the NIH Office of Research on Women's Health to my successors, that women's health research and career programs including those that are interdisciplinary in nature, the inclusion of women and minorities in clinical research, and efforts to address sex differences in basic investigation are firmly secured into the fabric of the NIH. And, I have further expectations that in the future, the ideals that led to the establishment of the Office will only become strengthened and more fully appreciated for their importance to the scientific mission of the NIH and the health and health care of women and their families.

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health

August 2011

Appendix G:
Catalog of Disease Registries, Databases, and Biomedical Information Systems

Project/Resource Title	Admin IC	Funding ICs	Institution
3D Atlas & Database o fMurine Urogenital Development	NIDDK	NIDDK	Medical Research Council
3D Domains	NLM	NLM	NLM
3D Slicer Registration Case Library	NIBIB	NIH Roadmap (NIBIB, NINDS, NHLBI, NIGMS, OD)	Brigham and Women's Hospital
Adult Acute Liver Failure Study Group (ALFSG)	NIDDK	NIDDK	University of Texas
AFINITI - An Augmented System for Neuroimaging Followup	NLM	NLM	MethodistHospitalResearchInstitute
AIDSInfo / InfoSIDA	NLM	NLM	NLM
Alaska Native Stroke Registry	NINDS	NINDS	Alaska Native Tribal Health Consortium
Alcohol Policy Information System (APIS)	NIAAA	NIAAA	CDM Group, Inc.
Algorithm and genome-wide database of functional siRNAs	NHGRI	NHGRI/NLM	Cellecta, Inc.
ALTBIB: Bibliography on Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing	NLM	NLM	NLM
Alzheimer's Disease Neuroimaging Initiative (ADNI)	NIA	NCRR, NIA, NIBIB, NIMH, NINDS, NINR	University of California, San Francisco
Alzheimer's Disease Patient Registry (ADPR)	NIA	NIA	Group Health Cooperative
Alzheimer's Disease Patient Registry (ADPR)	NIA	NIA	Mayo Clinic College of Medicine, Rochester
Analysis and Annotation of the E. coli Genome Sequence	NIGMS	NIGMS	University of Miami School of Medicine
Andrean Global Health Informatics Research and Training Center	FIC	FIC, OD	Universidad Peruana Cayetano Heredia
Antidepressants, Concurrent Treatments, and Completed Suicide in VA Registry Data	NIMH	NIMH	University of Michigan at Ann Arbor
AphasiaBank: A Shared Database for the Study of Aphasic Communication	NIDCD	NIDCD	Carnegie-Mellon University
Asia-Pacific HIV Observational Database (APHOD)	NIAID	NIAID, NCI, NICHD	Foundation for AIDS Research
Aspergillus Genome Database	NIAID	NIAID, NCBB	Stanford University

Project/Resource Title	Admin IC	Funding ICs	Institution
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 System To Monitor Medical Device Safety	NLM	NLM	Brigham and Women's Hospital
Baseline Microdata for Analysis of U.S. Demographic Change	NICHD	NICHD	University of Minnesota Twin Cities
Beta Cell Biology Consortium (BCBC)	NIDDK	NIDDK	Multiple
BIG Health	NCI	NCI	NCI
Biodefense and Emerging Infections Research Resources Repository (BEI)	NIAID	NIAID	ATCC
Bioisis	NCI	NCI	Berkeley National Laboratory
Biological Biochemical Image Database (BBID)	NIA	NIA	NIA
Biological Magnetic Resonance Data Bank	NLM	NLM	University of Wisconsin Madison
Biomedical Informatics Research Network (BIRN) Data Repository	NCRR	NCRR	University of California, San Diego
Biomedical Informatics Research Network (BIRN) Data Repository	NCRR	NCRR	University of California, San Diego
Biomedical Research Informatics for Global Health Training (BRIGHT) Program	FIC	FIC	University of California San Diego
Biomedical Translational Research Information System (BTRIS)	CC	CC	NIH Clinical Center
Biospecimen Research Database	NCI	NCI	NCI
Breast and Colon Cancer Family Registries	NCI	NCI	Multiple
Breast Cancer Information Core (BIC)	NGHRI	NGHRI	NHGRI
Breast Cancer Surveillance Consortium	NCI	NCI	Multiple
Building and Validating Location Proteomics Databases	NIGMS	NIGMS, NIBIB	Carnegie-Mellon University
CABIG Enterprise	NCI	NCI	NCI
CADD Group Chemoinformatics Tools and User Services	NCI	NCI	NCI
California Health Interview Survey	NCI	NCI	UCLA Center for Health Policy ResearchExternal Web Site Policy, the California Department of Public Health, and the California Department of Health Care Services.
California Parkinson's Disease Registry	NIEHS	NIEHS	Multiple
Cancer Chromosomes	NCI, NML	NCI, NLM	NCI, NML
Cancer Control P.L.A.N.E.T.	NCI	NCI	NCI
Cancer Genetics Network	NCI	NCI	Massachusetts General Hospital, a Harvard Medical School teaching affiliate

Project/Resource Title	Admin IC	Funding ICs	Institution
Cancer Genome Anatomy Project (CGAP)	NCI	NCI	NCI
Cancer Intervention and Surveillance Modeling Network (CISNET)	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
Candidate-gene Association Resource (CARe)	NHLBI	NHLBI	Broad Institute
Cardiac Arrest and Trauma Registry	NHLBI	NHLBI	University of Washington
Cardiac Atlas Project: Establishment of a Cardiac MRI Database	NHLBI	NHLBI, NIGMS	University of Auckland
Cardiovascular Research Grid (CVRG)	NHLBI	NHLBI	Johns Hopkins University
Carolina Mammography Registry	NCI	NCI	University of North Carolina Chapel Hill
CCASAnet: Caribbean, Central and South America Network	NIAID	NIAID	Vanderbilt Univ School of Med
CDC Data Resource Center	NIDCR	NIDCR, CDC	NIDCR, CDC
Center for Collaborative Genomic Studies on Mental Disorders	NIMH	NIMH	Washington University in St. Louis, Rutgers University, University of Southern California
Center for International Blood and Marrow Transplant Research (CIBMTR)	NCI	NCI, NHLBI, NIAID	Medical College of Wisconsin & National Marrow Donor Program
Center for Zebrafish Chromatin and Epigenetics	NICHD	NICHD	University of Utah
Central NIDDK Repository for Biosamples and Data	NIDDK	NIDDK	NIDDK
Chemical Carcinogenesis Research Information System (CCRIS)	NCI	NCI	NCI
Chemical Effects in Biological Systems	NIEHS	NIEHS	NIEHS
ChemIDPlus	NLM	NLM	NLM
Classification of Laws Associated with School Students	NCI	NCI	NCI
Clinical Outcomes Research: An Endoscopic Data Base	NIDDK	NIDDK	Oregon Health and Science University
Clinical Trials Dissemination Library	NIDA	NIDA	Washington University
Clinical Trials Public Data Share Website	NIDA	NIDA	The EMMES Corporation
ClinicalTrials.gov	NLM	NLM	NLM
Clone Registry	NLM	NLM	NLM
CNV (Copy Number Variation) Atlas of Human Development	OD	NICHD	Emory University
Cochrane Collaboration Cam Field: Resource For Research	AT	AT	University of Maryland Baltimore

Project/Resource Title	Admin IC	Funding ICs	Institution
Cochrane Collaboration Cam Field: Resource For Research	NCCAM	NCCAM	University of Maryland Baltimore
Cohort Registry of Type 1 Diabetes	NIDDK	NIDDK	University of Wisconsin Madison
Collaborative Islet Transplant Registry (CITR)	NIDDK	NIDDK	EMMES Corp.
Collaborative Studies on Genetics of Alcoholism (COGA) Database	NIAAA	NIAAA	SUNY Downstate Medical Center
Colorectal Cancer Mortality Projections	NCI	NCI	NCI
COMBINE (Combining Medications and Behavioral Interventions) Data Set	NIAAA	NIAAA	NIAAA
Community Epidemiology Work Group (CEWG)	NIDA	NIDA	NIDA
Comparative Toxicogenomics Database (CTD)	NIEHS	NIEHS/NLM	Mount Desert Island Biological Lab
Completion of Human Embryo Sections On DVDs	NICHD	NICHD	Louisiana State Univ HSC New Orleans
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
Computer-based Patient Provider Communication About CAM Use	NICHD	NICHD	Transcendent International, LLC
Consensus Coding Sequence Regions (CCDS) Database	NLM	NLM	NLM
Conserved Domain Architecture Retrieval Tool (CDART)	NLM	NLM	NLM
Continued Development of Stanford Microarray Database	NHGRI	NHGRI	Stanford University
Coordinating and Bioinformatics Unit for the AMDCC/MMPC (Animal Models of Diabetic Complications Consortium/ Mouse Metabolic Phenotyping Centers)	NIDDK	NIDDK	Medical College of Georgia
Core Database of Interacting Proteins (DIP)	NIGMS	NIGMS	University of California, Los Angeles
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	NINDS	NINDS, NIMH	Allen Institute for Brain Science
Creation of A Marine Natural Products Library To Enhance Life Science Research	NCCAM	NCCAM	Florida Atlantic University
CRW Project: A Comparative Database of RNA Molecules	NIGMS	NIGMS	University of Texas Austin

Project/Resource Title	Admin IC	Funding ICs	Institution
DAIDS HIV/OI/TB Therapeutics Database	NIAID	NIAID	Gryphon Scientific, LLC
DailyMed	NLM	NLM	NLM
Data Management and Coordinating Center (DMCC)	NINDS	ORDR	University of South Florida
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 Genotypes and Phenotypes (dbGaP)	NLM	NLM	NLM
Database of Longitudinal Studies	NIA	NIA	NIA
Database of Major Histocompatibility Complex (dbMHC)	NLM	NLM	NLM
Database of Single Nucleotide Polymorphisms (dbSNP)	NLM	NLM	NLM
Databases and Data Models Enabling Neuroinformatics	NIMH	NIMH, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCR, NINDS, NLM	Weill Medical College of Cornell University
Development of a National Incompatible Kidney Transplant Registry	NIDDK	NIDDK, NLM, OD	Johns Hopkins University
Development of a Pediatric Mylelodysplastic Syndrome Patient Registry	NIDDK	NIDDK	Children's Hospital 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 NIAAA Correlational Database	NIAAA	NIAAA	Genome Exploration, Inc.
Development of the Mouse Cochlea Database	NIDCD	NIDCD, NCI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIMH, NLM	University of Minnesota Twin Cities
Development of the Pediatric IBD Behavioral Health Registry	NICHD	NICHD, NIDDK, NIMH	Rhode Island Hospital (Providence, RI)
Development of the www.EcoliCommunity.org Information Resource	NIGMS	NIGMS	Purdue University West Lafayette
Developmental and Reproductive Toxicology Database (DART)	NLM	NLM	NLM

Project/Resource Title	Admin IC	Funding ICs	Institution
Diabetes Genome Anatomy Project (DGAP)	NIDDK	NIDDK	NIDDK
Diabetic Foot and Pressure Ulcer Databank	NLM	NLM, NIAMS	New York University School of Medicine
Diazeniumdiolate Database	NCI	NCI	NCI
Dietary Supplement Ingredients Database	OD/ODS	OD/ODS, FDA, CDC, NIST	OD/ODS
Dietary Supplements Labels Database	NLM	NLM	NLM
DIRLINE (Online Directory of Health Organizations)	NLM	NLM	NLM
DNA Polymerase Database	NIGMS	NIGMS	New England Biolabs, Inc.
Early Detection Research Network (EDRN)	NCI	NCI	Multiple
East Africa IEDEA Regional Consortium	NIAID	NIAID	Indiana University
East African Network for Informatics Training	FIC	FIC, NHGRI	Regenstrief Institute
EM Open Connectome Project	NIBIB	NIBIB	Johns Hopkins University (subcontract to Harvard)
Enhancements To A Human Embryo, Serial-Section Database	NLM	NLM	Louisiana State Univ HSC New Orleans
Enhancing the JaxMice Database Resource	NLM	NLM	Jackson Laboratory
ENRICH project in Colombia	FIC	FIC	University of Pittsburgh
Entrez Gene	NLM	NLM	NLM
Entrez Genome	NLM	NLM	NLM
Entrez Nucleotide	NLM	NLM	NLM
Entrez PopSet	NLM	NLM	NLM
Entrez Protein	NLM	NLM	NLM
Entrez Taxonomy	NLM	NLM	NLM
Environmental Polymorphisms Registry (EPR)	NIEHS NCRR	NIEHS NCRR	Integrated Laboratory Systems, Inc., University of North Carolina
Ethnomed Knowledge Management Grant	NLM	NLM	University of Washington
Eukaryotic Pathogen Database Resources (EuPathDB)	NIAID	NIAID	Strategies WDK
Extended Thermodynamic Database for Modified Oligonucleotides	NIGMS	NIGMS	DNA Software, Inc.
FaceBase: A Resource for Craniofacial Researchers	NIDCR	NIDCR	University of Iowa; and University of Pittsburgh
Finding Cancer Statistics	NCI	NCI	NCI
FITBIR (Federal Interagency Traumatic Brain Injury Research) Informatics System	NINDS	NINDS, DOD	NIH CIT
FLYBASE: A Drosophila Genomic and Genetic Database	NHGRI	NHGRI	Harvard University
Food Attitudes and Behavior Survey Project	NCI	NCI	NCI

Project/Resource Title	Admin IC	Funding ICs	Institution
Geisha, A Chicken Embryo Gene Expression Resource	NICHD	NICHD	University of Arizona
GenBank	NLM	NLM	NLM
Gene Expression Database for Mouse Development	NICHD	NICHD	Jackson Laboratory
Gene Expression Nervous System Atlas (GENSAT)	NINDS	NINDS	Rockefeller University
Gene Expression Nervous System Atlas (GENSAT)	NLM	NLM	NLM
Gene Regulation E. coli Database Integrated Modeling	NIGMS	NIGMS	Center for Genomic Sciences
GeneNetwork	NIAAA	NIAAA	University of Tennessee Health Sciences Center
Genetic Association Database	NIA, CIT	NIA, CIT	National Institutes of Health
Genetic Toxicology Databank (GENE-Tox)	NLM	NLM	EPA
Genetically Altered Animal Models Related to Heart, Lung, Blood, or Sleep	NHLBI	NHLBI	NHLBI
Genetics Home Reference	NLM	NLM	NLM
Genomic Database for Candida Albicans	NIDCR	NIDCR, NIAID	Stanford University
Genomic Database for the Yeast Saccharomyces	NHGRI	NHGRI	Stanford University
Genomic Datasets for Cancer Research	NCI	NCI	NCI
Genomics and Bioinformatics Software Tools	NCI	NCI	NCI
GEO (Gene Expression Omnibus)	NLM	NLM	NLM
Geographic Information System for Breast Cancer Studies on Long Island	NCI	NCI	Multiple
Glycomics/Legacy Informatics Resources for Glycomics	NIGMS	NIGMS	Massachusetts Institute of Technology
Grid-Enabled Measures	NCI	NCI	NCI
Haz-Map: Occupational Exposure to Hazardous Agents Database	NLM	NLM	NLM
HBV (Hepatitis B Virus) Research Network Database Protocol and Clinical Trial Study Proposals	NIDDK	NIDDK	University of California, Los Angeles
Health Disparities Calculator (HD*Calc)	NCI	NCI	NCI
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
Health Services/Technology Assessment Text (HSTAT)	NLM	NLM	NLM
Hereditary Causes of Nephrolithaisis and Kidney Failure	NIDDK	NIDDK	Mayo Clinic Rochester

Project/Resource Title	Admin IC	Funding ICs	Institution
Historical Elder Abuse Data & Annotated Bibliography	NLM	NLM	University of Iowa
HIV/SIV Database and Analysis Unit	NIAID	NIAID	NIAID
HIV-1/SIV Antibody Neutralization Assay Improvements and Database Development	NIAID	NIAID	Monogram Biosciences, Inc.
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 Exchange	NIDDK	NIDDK	National Disease Research Interchange
Human Nutrition Research and Information Management (HNRIM) Database	NIDDK	NIDDK	NIDDK
Human oral Microbiome Database (HOMD)	NIDCR	NIDCR	The Forsyth Institute
Images from the National Library of Medicine	NLM	NLM	NLM
ImmPort	NIAID	NIAID	Northrup Grummon
Immune Epitope Database and Analysis Program	NIAID	NIAID	La Jolla Inst for Allergy & Immunology
Infectious Disease Genomics and Bioinformatics Training in Brazil	FIC	FIC	University of Georgia
Influenza Research Database	NIAID	NIAID	Northrup Grummon Health IT, J. CraigVenter Institute; VecnaTechnologies; SAGE Analytica,Los Alamos National Laboratories
Influenza Virus Resource	NLM	NLM	NLM
Informatics Training Program in India	FIC	FIC	Vanderbilt
Information Resources for Radiation Science	NCI	NCI	National Council On Radiation Protection & Measurements
Integrated Risk Information System (IRIS)	NLM	NLM	EPA
Integrating Data, Models, and Reasoning in Critical Care	NIBIB	NIBIB	Massachusetts Institute of Technology
Interactive Craniofacial Normative Database (Phase II)	NIDCR	NIDCR	Praxis, Inc
Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)	NHLBI	NHLBI	University of Alabama at Birmingham
International Bibliographic Information on Dietary Supplements (IBIDS) Database	OD/ODS	OD/ODS, USDA	OD/ODS
International epidemiologic Database to Evaluate AIDS (West Africa) Core	NIAID	NIAID, NCI, NICHD	University of Bordeaux II
International Epidemiologic Databases to Evaluate AIDS (IEDEA) in central Africa (Region 9)	NIAID	NIAID, NCI, NICHD	Research Triangle Institute

Project/Resource Title	Admin IC	Funding ICs	Institution
International Mouse Strain Resource (IMSR)	NLM	NLM	Jackson Laboratory
International Network and Registry for Thrombotic Microangiopathy (TMA	NIDDK	NIDDK	Feinstein Institute for Medical Research
International Neuroinformatics Coordinating Facility (INCF)	AT	AT	
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
Kaiser Permanente Autoimmune Disease Registry	NIAID	NIAID, NIAMS, NIDDK, OD	Kaiser Foundation Research Institute
Knowledge-Based Resource for Linking Animal Models To Human Disease	OD/ORIP	OD/ORIP	Princeton University, Oregon Health and Science University
LactMed (Drugs and Lactation Database)	NLM	NLM	NLM
Large Databases of Small Molecules - Drug Development Tool and Public Resource	NCI	NCI	NCI
Library of Standardized Patient Registry Questions for Rare Diseases	NLM	NLM, OD	University of South Florida
Limited Access Datasets from NIMH Clinical Trials	NIMH	NIMH	NIMH
Linking Data Sources from the Autism Genetic Resource Exchange (AGRE) with NDAR	NIMH	NIMH, NICHD	Autism Speaks, Inc.
LONI (Laboratory of Neural Imaging) Image Data Archive	NIBIB	NIBIB	University of California, Los Angeles
Malaria Research Resources	NLM	NLM	NLM
Medicinal Plants of Antiquity: a Computerized Database	NCCAM	NCCAM	Smithsonian Institution
Micro-Manager	NIBIB	NIBIB	UCSF
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
MouseCyc: A Biochemical Pathway Database for the Mouse	NHGRI	NHGRI	Jackson Laboratory
Mutant Mouse Resource and Research Centers Informatics, Coordination and Service Center	OD/ORIP	OD/ORIP	UC Davis

Project/Resource Title	Admin IC	Funding ICs	Institution
Nanomaterial Registry	NIBIB	NIBIB, NIEHS, NCI	RTI International
National Addiction & HIV Data Archive Program	NIDA	NIDA	University of Michigan
National Cancer Image Archive	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 and Science University
National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	NIAAA	NIAAA	NIAAA
National Health and Alcohol Study (NHAS)	NIAAA	NIAAA	NIAAA
National Health and Nutrition Examination Survey	NCI	multiple	National Center for Health Statistics(NCHS), Centers for Disease Control and Prevention (CDC)
National Health Interview Survey (CDC)	AT	AT	
National Health Interview Survey - Cancer Control Supplement	NCI	NCI, CDC	National Center for Health Statistics(NCHS), Centers for Disease Control and Prevention (CDC)
National Information Resource on Ethics & Human Genetics	NHGRI	NHGRI	Georgetown University
National Longitudinal Alcohol Epidemiologic Survey (NLAES)	NIAAA	NIAAA	NIAAA
National NeuroAIDS Tissue Consortium	NIMH	NIMH	NIMH
National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE)	NEI	NEI	NEI
National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members	NHLBI	NIAMS, NINDS	University of Rochester, NY
National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)	NHLBI	NHLBI, NIAMS	RTI International
National Resource for Postmortem Brain Research	NIMH	NIHM, NINDS	McLean Hospital - Harvard Medical School
NCBI Biosystems Database	NLM	NLM	NLM
NEIBANK: EST Analysis and Bioinformatics for Ocular Genomics	NEI	NEI	NEI
Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC)	NIBIB	NIBIB, NCCAM, NCRR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, 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

Project/Resource Title	Admin IC	Funding ICs	Institution
NIA Genetics of Alzheimer's Disease Data Storage Site	NIA	NIA	Washington University in St. Louis
NIA Primate Aging Database	NIA	NIA	University of Wisconsin, Madison
NIAID HIV Protein Interaction Database	NIAID	NCBI, NIAID	DAIDS/NIAID & NCBI
NIBIB-RSNA (Radiological Society of North America) RadLex Ontology	NIBIB	NIBIB	Radiological Society of North America (RSNA)
NIDA Center for Genetics Research	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 Biosample Repository	NIDDK	NIDDK	Fisher Bioservices
NIDDK Data Repository	NIDDK	NIDDK	RTI International
NIDDK Genetics Repository	NIDDK	NIDDK	Rutgers University
NIEHS Chemical Effects in Biological Systems (CEBS) Knowledge Base	NIEHS	NIEHS	NIEHS
NIH AIDS Research and Reference Reagent Program	NIAID	NIAID	Fisher BioServices
NIH Blueprint Neuroscience Information Framework	NIDA	NIDA	University of California, San Diego
NIH Human Embryonic Stem Cell (hESC) Registry	OSP/OD	OSP/OD	OSP/OD
NIH Pediatric MRI Data Repository Clinical Coordinating Center	NICHD	NIDA, NIMH, NICHD	Washington University
NIH Pediatric MRI Data Repository Data Coordinating Center	NIMH	NIDA, NIMH, NICHD	McGill University/ Neurovision
NIH Stem Cell Data Management System	NINDS	NINDS	NIH Stem Cell Unit; NINDS Division of Intramural Research
NIH Tetramer Core Facility	NIAID	NIAID, NCI	Emory/Yerkes
NIMH Genetics Repository	NIMH	NIMH	Washington University in St. Louis
NIMH HIV Brain Bank - National Coordinating office (NCO)	NIMH	NIMH	Emmes Corporation
NINDS Common Data Elements	NINDS	NINDS	KAI Research, Inc.
NINDS Human Genetics Resource Center	NINDS	NINDS	Coriell Institute
NINDS/UC Davis NeuroMab Hybridoma Facility	NINDS	NINDS, NIMH, OD, ORDR	University of California, Davis
NLM Catalog	NLM	NLM	NLM
North American AIDS Cohorts Collaboration on Research and Design	NIAID	NIAID	Johns Hopkins University
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

Project/Resource Title	Admin IC	Funding ICs	Institution
Online Mendelian Inheritance In Man (OMIM)	NLM	NLM	NLM
Osteoarthritis Initiative (OAI) Data Coordination Center	NIAMS	NIBIB, NIA, NCCAM, NIDCR, ORWH, NIMHD	University of California, San Francisco
PACEmaker & Beta-Blocker Therapy Post-Myocardial Infarct	NHLBI	NHLBI	Northwestern University at Chicago
Parkinson's Disease Data Organizing Center [PD-DOC]	NINDS	NINDS	University of Rochester
PathoSystems Resource Integration Center (PATRIC)	NIAID	NIAID	Virginia Bioinformatics Institute
Pathway Interaction Database Support	NCI	NCI	NCI
PaVE-Papillomavirus Bioinformatics Resource	NIAID	NIAID	NIH
Pediatric Cardiomyopathy Registry	NHLBI	NHLBI	University of Miami School of Medicine
Pediatric Imaging, Neurocognition, and Genetics (PING)	NIDA	NIDA	University of California, San Diego
Peptidome	NLM	NLM	NLM
Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB)	NIGMS	NIGMS, NHGRI, NLM	Stanford University
PhenoGen	NIAAA	NIAAA	University of Colorado, Denver
Plan for Extracting Intraoperative Anesthesia Data to the ACS NSQIP Database	NLM	NLM	American College of Surgeons
Population Database for the United States in 1880	NICHD	NICHD	University of Minnesota
Prevention of Renal Damage in Primary Hyperoxaluria	NIDDK	NIDDK	Mayo Clinic Rochester
Probe	NLM	NLM	NLM
Profiles in Science	NLM	NLM	NLM
Project MATCH Data Base	NIAAA	NIAAA	University of Connecticut Health Center
Prostate Cancer Prevention Trial (PCPT) Biorepository	NCI	NCI	Southwest Cooperative Oncology Group (SWOG)
Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Biorepository	NCI	NCI	NCI
Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Biorepository	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; University of California, San Diego
PubChem	NLM	CF	NLM

Project/Resource Title	Admin IC	Funding ICs	Institution
Public HIV Drug Resistance Database	NIAID	NIAID	Stanford University
Public Use Data On Mexican Immigration	NICHD	NICHD	Princeton University
PubMed Centra	NLM	NLM	NLM
Pubmed/Medline	NLM	NLM	NLM
Radiation Event Medical Management	NLM	NLM	NLM
Rapid Research Notes Archive	NLM	NLM	NLM
Rat Genome Database	NHLBI	NHLBI, NCI, NEI, NHGRI, NIA, NIAAA, NICHD, NIDCD, NIDDK, NIEHS, NIMH, NINDS, NIBIB	Medical College of Wisconsin
Reference Image Database to Evaluate Response (RIDER)	NCI	NIBIB	MSKCC, MDACC, University of Washington, Duke, University of Michigan
Registry and Surveillance for Hemoglobinopathies	NHLBI	NHLBI	CDC
Registry Study of Parkinson's Disease in Denmark	NIEHS	NIEHS, NINDS	University of California, Los Angeles
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 Resource for Complex Physiologic Signals	NIGMS	NIGMS, NIBIB	Beth Israel Deaconess Medical Center
Restriction Enzyme Database (REBASE)	NLM	NLM	New England Biolabs, Inc.
Retrovirus Epidemiology Study II (REDS II)	NHLBI	NHBLI	Westat
Rheumatoid Arthritis in African Americans Registry	NIAMS	NIAMS	University of Alabama at Birmingham
RxNorm	NLM	NLM	NLM
Salivary Gland Molecular Anatomy Project	NIDCR	NIDCR	NIDCR
Salivary Proteome Wiki Project	NIDCR, CIT	NIDCR, CIT	NIH
Sea Urchin Genome Database (SpBase)	NICHD	NICHD	California Institute of Technology
Secure Web-Based Intake And Tracking Tools For Cam Research And Clinical Practice	AT	AT	Reliefinsite.com, LLC
SEER-Medicare Data	NCI	NCI	NCI
SEER-Medicare Health Outcomes Survey Linked Database	NCI	NCI	NCI
Selenium and Vitamin E Cancer Prevention Trial (SELECT) Biorepository	NCI	NCI	Southwest Cooperative Oncology Group (SWOG)
SenseLab: Integration of Multidisciplinary Sensory Data	NIDCD	NIDCD, NINDS	Yale University
Sequence Read Archive (SRA)	NLM	NLM	NLM

Project/Resource Title	Admin IC	Funding ICs	Institution
Severe Chronic Neutropenia International Registry	NIAID	NIAID	University of Washington
Shared Database for the Study of Phonological Development	NICHD	NICHD	Carnegie-Mellon University
Shared Distributed Learning for Developing Medical Informatics Capacity in Africa	FIC	FIC	University of KwaZulu Natal
Shwachman-Diamond Syndrome International Registry and Repository	NIAID	NIAID, NICHD	Fred Hutchinson Cancer Research Center
Small Area Estimates for Cancer Risk Factors & Screening Behaviors	NCI	NCI	NCI
Spatially Oriented Database for Digital Brain Images	NIA	NIA, NIHM	University of Pennsylvania
State Cancer Profiles	NCI	NCI, CDC	NCI
Structural Biology Information Resources	NLM	NLM	NLM
Surveillance, Epidemiology and End Results (SEER)	NCI	NCI	NCI
Surveillance, Epidemiology and End Results (SEER)	NCI	NCI	NCI
The Cancer Imaging Archive (TCIA)	NCI	NCI	NCI
The Manhattan HIV Brain Bank	NIMH	NIMH, NINDS	Mount Sinai School of Medicine
The United States Immunodeficiency Network, (USIDNET)	NIAID	NIAID	Immune Deficiency Foundation
Tobacco Use Supplement to the Current Population Survey	NCI	NCI	U.S. Census Bureau
Toxics Release Inventory	NLM	NLM	EPA
TOXLINE (Toxicology Literature Online)	NLM	NLM	NLM
TOXMAP	NLM	NLM	EPA
Trace Archive	NLM	NLM	NLM
Trace Assembly Archive	NLM	NLM	NLM
Transcriptional Atlas of Human Brain Development	NIMH	NIMH, NINDS, NIDA	Allen Brain Institute, Yale University, University of Southern California
Translational Informatics for Global Health in Argentina	FIC	FIC, NLM	Oregon Health & Sciences University
Transporter Classification Database (TCDB)	NIGMS	NIGMS, NIAID, NIBIB, NLM	University of California, San Diego
Trauma-Related Database	NIGMS	NIGMS	Massachusetts General Hospital
UMLS (Unified Medical Language System)	NLM	NLM	NLM
UMLS-Based Archive System for Digital Resources	NLM	NLM	Johns Hopkins University
UniGene	NLM	NLM	NLM
UniProt Protein Sequence and Function Knowledgebase	NHGRI	NHGRI, NCRR, NIDCR, NIGMS, NIMH, NLM	European Molecular Biology Laboratory
UniSTS (Unified Sequence Tagged Sites)	NLM	NLM	NLM

Project/Resource Title	Admin IC	Funding ICs	Institution
United States Renal Data System (USRDS)	NIDDK	NIDDK	NIDDK
User-Friendly System Dynamics Analysis Tools For Translational Mind-Body Research	AT	AT	DYNADX Corporation
Utility of a New Database to Study Drug Safety during Pregnancy	NICHD	NICHD	Brigham and Women's Hospital
VectorBase (Invertebrate Vectors of Human Pathogens)	NIAID	NIAID	NIAID
Virus Pathogen Resource (ViPR)	NIAID	NIAID	Northrup Grummon Health IT, J. CraigVenter Institute; VecnaTechnologies
Wireless Information System for Emergency Responders (WISER)	NLM	NLM	NLM
Wisconsin Registry for Alzheimer Prevention: Biomarkers of Preclinical AD	NIA	NIA	University of Wisconsin, Madison
Xenbase: a Xenopus Model Organism Database	NICHD	NICHD, NHGRI	University of Calgry
XNAT Open Source Informatics for Imaging Research	NIBIB	NIBIB	Washington University
ZFIN: The Zebrafish Model Organism Database	NHGRI	NHGRI, NICHD, NIDDK, NIGMS	University of Oregon

Appendix H:
Funding for Chronic Diseases and Organ Systems

NIH Categorical Spending: http://report.nih.gov/categorical_spending.aspx

Chronic Disease and Organ Systems Funding			
	FY 2010 Actual (Non ARRA)	FY 2010 Actual (ARRA)	FY 2011 Actual
Auditory System			
Otitis Media	$19	$2	$15
Brain Disorders	$3,847	$619	$3,864
ALS	$47	$12	$44
Alzheimer's Disease	$450	$79	$448
Aphasia	$21	$1	$21
Autism	$160	$58	$169
Batten Disease	$5	$1	$4
Brain Cancer	$274	$36	$280
Cerebral Palsy	$19	$3	$23
Epilepsy	$134	$27	$152
Frontotemporal Dementia (FTD)	$18	$1	$23
Pick's Disease	$2	$0	$3
Huntington's Disease	$65	$7	$56
Injury - Traumatic brain injury	$85	$9	$81
Mental Retardation (Intellectual and Developmental Disabilities (IDD))	$311	$87	$333
Autism	$160	$58	$169
Down Syndrome	$22	$6	$20
Fragile X Syndrome	$25	$4	$29
Fetal Alcohol Syndrome	$33	$5	$36
Multiple Sclerosis	$133	$18	$122
Parkinson's Disease	$154	$18	$151
Rett Syndrome	$13	$2	$12
Reye's Syndrome	$0	$0	$0
Schizophrenia	$276	$63	$264
Tourette Syndrome	$7	$0	$5
Tuberous Sclerosis	$20	$2	$20
Cancer	$5,823	$803	$5,448
Brain Cancer	$274	$36	$280
Breast Cancer	$763	$61	$715
Cervical Cancer	$93	$8	$119

Childhood Leukemia	$55	$12	$59
Colo-rectal Cancer	$291	$26	$313
HPV and/or Cervical Cancer Vaccine	$25	$2	$24
Liver Cancer	$102	$10	$74
Lung Cancer	$201	$22	$221
Lymphoma	$195	$14	$199
Hodgkin's Disease	$24	$1	$20
Neuroblastoma			$25
Ovarian Cancer	$122	$10	$138
Pancreatic Cancer			$112
Prostate Cancer	$331	$31	$284
Uterine Cancer	$26	$4	$40
Cardiovascular	$2,144	$398	$2,049
Atherosclerosis	$544	$104	$475
Heart Disease	$1,329	$235	$1,236
Heart Disease- Coronary Heart Disease	$457	$80	$437
Hypertension	$251	$50	$240
Dental /Oral and Craniofacial Disease	$497	$67	$501
Temporomandibular Muscle/Joint Disorder (TMJD)	$16	$1	$18
Diabetes	$1,046	$153	$1,076
Digestive Diseases	$1,657	$228	$1,698
Digestive Diseases - (Gallbladder)	$5	$0	$4
Digestive Diseases - (Peptic Ulcer)	$30	$3	$18
Inflammatory Bowel Disease	$106	$19	$113
Crohn's Disease	$66	$12	$67
Colo-Rectal Cancer	$291	$26	$313
Liver Diseases	$627	$85	$623
Chronic Liver Disease and Cirrhosis	$284	$45	$303
Liver Cancer	$102	$10	$74
Hepatitis	$204	$25	$208
Hepatitis - A	$4	$0	$4
Hepatitis - B	$66	$4	$58
Hepatitis - C	$100	$12	$114
Endocrine System			
Estrogen	$231	$23	$227
Diethylstilbestrol (DES)	$4	$1	$3
Eye Disease and Disorders of Vision	$817	$110	$831
Macular Degeneration	$104	$9	$105

Hematology	$961	$141	$1,006
Childhood Leukemia	$55	$12	$59
Cooley's Anemia	$20	$3	$20
Septicemia	$90	$17	$91
Sickle Cell Disease	$73	$12	$65
Immune System			
Allergic Rhinitis (Hay Fever)	$3	$1	$7
Asthma	$244	$33	$221
Autoimmune Disease	$856	$125	$869
Inflammatory Bowel Disease	$106	$19	$113
Lupus	$112	$15	$106
Multiple Sclerosis	$133	$18	$122
Myasthenia Gravis	$8	$3	$9
Psoriasis	$13	$3	$10
Scleroderma	$19	$2	$25
Childhood Leukemia	$55	$12	$59
Food Allergies			$33
Lymphoma	$195	$14	$199
Hodgkin's Disease	$24	$1	$20
Vaccine Related	$1,737	$222	$1,717
HPV and/or Cervical Cancer Vaccine	$25	$2	$24
Malaria Vaccine	$41	$4	$39
Vaccine Related (AIDS)	$535	$27	$550
Biodefense	$1,794	$221	$1,803
Tuberculosis Vaccine	$13	$3	$17
Integumentary System			
Psoriasis	$13	$3	$10
Scleroderma	$19	$2	$25
Kidney Disease	$552	$98	$557
Polycystic Kidney Disease	$35	$6	$42
Urologic Diseases	$563	$56	$542
Interstitial Cystitis	$12	$1	$13
Prostate Cancer	$331	$31	$284
Lung	$1,269	$207	$1,278
Acute Respiratory Distress Syndrome	$110	$22	$96
Asthma	$244	$33	$221
Chronic Obstructive Pulmonary Disease	$118	$15	$108
Cystic Fibrosis	$86	$13	$79
Emphysema	$23	$9	$22
Lung Cancer	$201	$22	$221

Perinatal - Neonatal Respiratory Distress Syndrome	$31	$3	$37
Pneumonia	$93	$17	$117
Mental Health	$2,246	$334	$2,275
Autism	$160	$58	$169
Attention Deficit Disorder (ADD)	$66	$15	$55
Depression	$420	$50	$426
Schizophrenia	$276	$63	$264
Musculoskeletal System			
Skeletal Muscle (former name: Muscular System)			
Muscular Dystrophy	$74	$12	$75
Myotonic Dystrophy	$10	$2	$9
Duchenne/Becker Muscular Dystrophy	$33	$5	$32
Facioscapulohumeral Muscular Dystrophy	$5	$1	$6
Myasthenia Gravis	$8	$3	$9
Spinal Muscular Atrophy	$16	$3	$19
Skeletal System			
Osteogenesis Imperfecta	$8	$4	$9
Osteoporosis	$181	$23	$179
Paget's Disease	$1	$0	$1
Joints, Ligaments, and Connective Tissues			
Temporomandibular Muscle/Joint Disorder (TMJD)	$16	$1	$18
Neurosciences	$5,515	$794	$5,548
Reproductive System			
Cervical Cancer	$93	$8	$119
Ovarian Cancer	$122	$10	$138
Prostate Cancer	$331	$31	$284
Uterine Cancer	$26	$4	$40
Vulvodynia	$2	$1	$2
Adolescent Sexual Activity	$80	$7	$69
Teenage Pregnancy	$22	$5	$19
Contraception /Reproduction	$419	$56	$415
Endometriosis	$15	$1	$14
Fibroid tumores (Uterine)	$12	$2	$12
Infertility	$76	$16	$74
Chronic Fatigue Syndrome	$6	$0	$6
Pain Research			
Fibromyalgia	$9	$0	$11

Headaches	$18	$1	$21
Migraines	$15	N/A	$16
Pain Conditions - Chronic	$360	$44	$386
Vulvodynia	$2	$1	$2

Appendix I:
Acronyms

ABCA1	ATP-binding Cassette Transporter
ACC	Autism Coordinating Committee
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Autism Centers of Excellence
ACTTION	Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks
AD	Alzheimer's Disease
ADC	Alzheimer's Disease Center
ADCS	Alzheimer's Disease Cooperative Study
ADGC	Alzheimer's Disease Genetics Consortium
ADHD	Attention-deficit/Hyperactivity Disorder
ADNI	Alzheimer's Disease Neuroimaging Initiative
AHEAD	Action for Health in Diabetes
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immunodeficiency Syndrome
ALL	Acute Lymphoblastic Leukemia
ALS	Amyotrophic Lateral Sclerosis
AMA	American Medical Association
AMD	Age-related Macular Degeneration
ARIC	Atherosclerosis Risk in Communities
Army STARRS	Army Study to Assess Risk and Resilience in Service Members
ARRA	American Recovery and Reinvestment Act
ASD	Autism Spectrum Disorder
BAER	Basal Adverse Event Report
BCBC	Beta Cell Biology Consortium
BCERC	Breast Cancer and the Environment Research Centers
BCERPs	Breast Cancer and the Environment Research Programs
BChE	Butyrylcholinesterase
BIRCWH	Building Interdisciplinary Careers in Women's Health
BIRN	Biomedical Informatics Research Network
BIRT	Building Interdisciplinary Research Teams
BLSA	Baltimore Longitudinal Study of Aging
BMD	Becker Muscular Dystrophy
BMI	Body Mass Index
BMSC	Bone Marrow Stromal Cells
BP	Blood Pressure
BPA	Bisphenol A
BPH	Benign Prostatic Hyperplasia

BTRC	Biomedical Technology Research Center
CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation
caBIG®	NCI cancer Biomedical Informatics Grid®
CAD	Coronary Artery Disease
CADET	Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases
caHUB	Cancer Human Biobank
CAM	Complementary and Alternative Medicine
CAMUS	Complementary and Alternative Medicine for Urological Symptoms
CARDIA	Coronary Artery Risk Development in Young Adults
CARe	Candidate Gene Association Resource
CATT	Comparison of AMD Treatment Trials
CBT	Cognitive Behavioral Therapy
CC	NIH Clinical Center
CCOP	Community Clinical Oncology Program
CDC	Centers for Disease Control and Prevention
CDEs	Common Data Elements
CE	Continuing Education
CEBS	Chemical Effects in Biological Systems
CEED	Center of Excellence in Eliminating Disparities
CER	Comparative effectiveness research
CERC	Centers of Excellence for Research on CAM
CERT	Community-Empowered Research Training
CETP	Cholesterylester Transfer Protein
CF	Cystic Fibrosis
CFH	Complement Factor H
CFRD	Cystic Fibrosis Related Diabetes
CFS	Chronic Fatigue Syndrome
CFS	Cleveland Family Study
CFSAC	Chronic Fatigue Syndrome Advisory Committee
CFTR	CF Transmembrane Conductance Regulator
CHARGE	Childhood Autism Risks from Genetics and Environment
CHI	Center for Human Immunology, Autoimmunity, and Inflammation
CHS	Cardiovascular Health Study
CIRT	Cardiovascular Inflammation Reduction Trial
CIT	Center for Information Technology
CJ-DATS	Criminal Justice-Drug Abuse Treatment Studies
CKD	Chronic Kidney Disease
CKiD	Chronic Kidney Disease in Children
CMD	Congenital Muscular Dystrophies
CMS	Centers for Medicare & Medicaid Services
CNRM	Center for Neuroscience and Regenerative Medicine
CNS	Centers for Neurodegeneration Science

CNV	Choroidal Neovascularization
COAG	Clarification of Optimal Anticoagulation through Genetics
COE	Centers of Excellence
COPD	Chronic Obstructive Pulmonary Disease
COPTR	Childhood Obesity Prevention and Treatment Research
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CORE	Centers for Cardiovascular Outcomes Research
CORT	Centers of Research Translation
CP/CPPS	Chronic Prostatitis/Chronic Pelvic Pain Syndrome
CPAG	Coalition of Patient Advocacy Groups
CPEA	Collaborative Programs of Excellence in Autism
CRADA	Cooperative Research and Development Agreement
CRCNS	Collaborative Research in Computational Neuroscience
CREST	Carotid Endarterectormy for Carotid Disease
CRIC	Chronic Renal Insufficiency Cohort
CRN	Cancer Research Network
CRP	C-reactive Protein
CSR	Center for Scientific Review
CT	Computer-assisted Tomography
CTC	Circulating Tumor Cells
CTC	Communities That Care
CTN	Clinical Trials Network
CTOT	Clinical Trials in Organ Transplantation
CTOT-C	Clinical Trials in Organ Transplantation in Children
C-TRIP	Cardiac Translational Research Implementation Program
CTSA	Clinical Translation Science Awards
CTSI	Clinical Translation Science Institutes
CVD	Cardiovascular Disease
CVRG	CardioVascular Research Grid
CVRN	Cardiovascular Research Network
dbGaP	Database of Genotype and Phenotype
DCCT	Diabetes Control and Complications Trial
DIAN	Dominantly Inherited Alzheimer's Network
DMCC	Data Management and Coordinating Center
DMD	Duchenne Muscular Dystrophy
DME	Diabetic Macular Edema
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DOHaD	Developmental Origins of Health and Disease
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcome Study

DRD4	D4 Receptor Gene
DTE	Device Thrombogenicity Emulator
E. coli.	Escherichia coli
EARLI	Early Autism Risk Longitudinal Investigation
EARLY	Early Adult Reduction of Weight through Lifestyle intervention
ED	Department of Education
EDIC	Epidemiology of Diabetes Interventions and Complications Study
EDRN	Early Detection Research Network
EITCs	Education and Information Transfer Cores
EKSIDDRCs	Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers
ELSI	Ethical, Legal and Social Implications
eMERGE	Electronic Medical Records and Genomics
EMR	Electronic Medical Record
ENaC	Epithelial Sodium Channel
ENCODE	ENCyclopedia Of DNA Elements
EPA	Environmental Protection Agency
EPR	Environmental Polymorphism Registry
F award	Fellowship
FAR	Federal Acquisition Regulation
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FHS	Framingham Heart Study
FIC	John E. Fogarty International Center
FITBIR	Federal Interagency TBI Research
fMRI	Functional Magnetic Resonance Imaging
FOA	Funding Opportunity Announcement
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal management of Multivessel Disease
FSGS	Focal Segmental Glomerulosclerosis
FSHD	Facioscapulohumeral muscular dystrophy
FY	Fiscal Year
GA	Geographic Atrophy
GAD	Glutamic Acid Decarboxylase
GDM	Gestational Diabetes Mellitus
GENSAT	Gene Expression Nervous System Atlas
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
GPRA	Government Performance and Results Act
GUDMAP	GenitoUrinary Development Molecular Anatomy Project
GWAS	Genome-Wide Association Studies
HANDLS	Healthy Aging in Neighborhoods of Diversity across the Life Span
HapMap	Haplotype Map

HbA1C	Hemoglobin A1C
HbF	Fetal Hemoglobin
HDAC2	Histone Deacetylase 2
HDACs	Histone Deacetylases
HGP	Human Genome Project
HHC	Health and Hospitals Corporation
HHS	Department of Health and Human Services
HIFU	High-Intensity Focused Ultrasound
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HIVAN	HIV-associated Nephropathy
HMO	Health Maintenance Organization
HOMD	Human Oral Microbiome Database
HPV	Human Papillomavirus
HRS	Health and Retirement Study
HRSA	Health Resources and Services Administration
IACC	Interagency Autism Coordinating Committee
IAN	Interactive Autism Network
IBCs	Intracellular Bacterial Communities
IBS	Irritable Bowel Syndrome
IC/PBS	Interstitial Cystitis/Painful Bladder Syndrome
ICAC	Inner-City Asthma Consortium
ICBP	Integrative Cancer Biology Program
ICs	Institutes and Centers
IDDs	Intellectual and Developmental Disabilities
IDE	Investigational Device Exemption
IGI	Image-guided Interventions
IHS	Indian Health Service
IND	Investigational New Drug
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IOM	Institute of Medicine
iPOP	Integrative Personal Omics Profile
IPRCC	Interagency Pain Research Coordinating Committee
iPS	Induced Pluripotent Stem Cell
IRB	Institutional Review Board
ISCHEMIA	Ischemic Heart Disease
ISS	International Space Station
ITP	Interventions Testing Program
JHS	Jackson Heart Study
K award	Career Development Award
LABS	Longitudinal Assessment of Bariatric Surgery
LAM	Lymphangioleiomyomatosis

LGMDs	Limb-girdle Muscular Dystrophies
LIPC	Hepatic Lipase Gene
LOTT	Long-term Oxygen Treatment Trial
LPL	Lipoprotein Lipase
LPS	Lipopolysaccharides
LTA4H	Leukotriene A4 Hydrolase
LUTD	Lower Urinary Tract Dysfunction
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MD	Muscular dystrophies
MDA	Malondialdehyde
MDS	Minimum Data Set
ME	Myalgic Encephalomyelitis
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MESA	Multi-Ethnic Study of Atherosclerosis
MHRN	Mental Health Research Network
MIDAS	Models of Infectious Disease Agent Study
miRNA	microRNA
MLV	Murine Leukemia Virus
modENCODE	Model ENCODE Project
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
MTF	Monitoring the Future
NACC	National Alzheimer's Coordinating Center
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NASH	Nonalcoholic Steatohepatitis
NCBC	National Centers for Biomedical Computing
NCCAM	National Center for Complementary and Alternative Medicine
NCCOR	National Collaborative on Childhood Obesity Research
NCI	National Cancer Institute
NCRAD	National Cell Repository for Alzheimer’s Disease
NCRR	National Center for Research Resources
NCS	National Children’s Study
NDAR	National Database for Autism Research
NDEP	National Diabetes Education Program
NEI	National Eye Institute
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NET-PD	NIH Exploratory Trials in PD
NExT	NCI Experimental Therapeutics Program
NHANES	National Health and Nutrition Examination Survey
NHATS	National Health and Aging Trends Study

NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIF	Neuroscience Information Framework
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIH CRM	NIH Center for Regenerative Medicine
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NIST	National Institute of Standards and Technology
NITRC	Neuroimaging Informatics Tools and Resources Clearinghouse
NKDEP	National Kidney Disease Education Program
NLM	National Library of Medicine
nm	Nanometers
NMR	Nuclear Magnetic Resonance
NRF2	Nuclear Factor Erythroid 2–Related Factor 2
NRSA	Ruth L. Kirschstein National Research Service Award
NYU	New York University
OAIC	Older Americans Independence Center
OASH	Office on Women's Health, Office of the Assistant Secretary for Health
OBSSR	Office of Behavioral and Social Sciences Research
OCPL	Office of Communications and Public Liaison
OER	Office of Extramural Research
OIR	Office of Intramural Research
OMAR	Office of Medical Applications of Research
OPPERA	Prospective Evaluation and Risk Assessment
OppNet	Basic Behavioral and Social Science Opportunity Network
ORBIT	Obesity Related Behavioral Intervention Trials
ORDR	Office of Rare Diseases Research
ORWH	Office of Research on Women's Health

P award	Program Projects or Centers Grants
PA	Program Announcement
PBRNs	Practice-based Research Networks
PCBs	polychlorinated biphenyls
PD	Parkinson's Disease
PedETrol	Pediatric ICUs at Emory Children's Center Glycemic Control
PEPH	Partnerships for Environmental Public Health
PET	Positron Emission Tomography
PFDN	Pelvic Floor Disorders Network
PFINDR	Phenotype Finder IN Data Resources
PGP	Proline-glycine-proline
PGRN	Pharmacogenetics Research Network
PharmGKB	Pharmacogenomics Knowledge Base
PHS	Public Health Service
PMC	PubMed Central
POATS	Prescription Opioid Addiction Treatment Study
POWER	Practice-Based Opportunity for Promotion of Weight Reduction
PPAR-γ	Peroxisome Proliferator-activated Receptor Gamma
PQ	Provocative Questions
PROMIS	Patient-Reported Outcomes Measurement Information System
PumpKIN	Pumps for Kids, Infants, and Neonates
QIBA	Quantitative Imaging Biomarkers Alliance
R award	Research Grant
RAAS	Renin-Angiotensin-Aldosterone System
RAID	Ranolazine Implantable Cardioverter-Defibrillator
RCMAR	Resource Centers for Minority Aging Research
RCMI	Research Centers in Minority Institutions
RDCRN	Rare Diseases Clinical Research Network
REGARDS	Reasons for Geographic and Racial Differences in Stroke
REMBRANDT	Repository of Molecular Brain Neoplasia Data
REVIVE IT	Randomized Evaluation of VAD Intervention before Inotropic Therapy
RICE	Rand IC Epidemiology
RIVUR	Randomized Intervention for Vesicoureteral Reflux
RNA	Ribonucleic Acid
ROMICAT II	Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography
RPE	Retinal Pigment Epithelium
SBIR	Small Business Innovation Research
SBIRT	Screening, Brief Intervention, and Referral
SCI	Spinal Cord Injury
SCORs	Specialized Centers of Interdisciplinary Research
SEER	Surveillance Epidemiology and End Results
SEP	Special Emphasis Panel

SES	Socioeconomic Status
SHHS	Sleep Heart Health Study
SHINE	Stimulating Hematology Investigation: New Endeavors
SIDS	Sudden Infant Death Syndrome
siRNA	Short-interfering RNA
SNP	Single-nucleotide Polymorphism
SOD3	Superoxide Dismutase
SPIROMICS	SubPopulations and InteRmediate Outcome Measures in COPD Study
SPORE	Specialized Programs of Research Excellence
SPOTRIAS	Specialized Program of Translational Research in Stroke
SPRINT	Systolic Blood Pressure Intervention
SRG	Scientific Review Group
STEP-UP	Short-Term Education Program for Underrepresented Persons
STICH	Surgical Treatment for Ischemic Heart Failure
STTR	Small Business Technology Transfer
SUI	Stress Urinary Incontinence
suPAR	Serum-soluble Urokinase Receptor
T award	Research Training Award
TARGET	Therapeutically Applicable Research to Generate Effective Treatments
TBI	Traumatic Brain Injury
TCGA	The Cancer Genome Atlas
TECS	Trial of Euglycemia in Cardiac Surgery
TEDDY	The Environmental Determinants of Diabetes in the Young
THAPCA	Therapeutic Hypothermia after Pediatric Cardiac Arrest
TIMP3	Metalloproteinase Inhibitor 3
TMJD	Temporomandibular Joint Disorders
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
tPA	Tissue Plasminogen Activator
T-R01	Transformative R01
TRND	Therapeutics for Rare and Neglected Diseases
UCD	Urea Cycle Defect
UDA	Urologic Diseases in America
UDP	Undiagnosed Diseases Program
UDS	Uniform Data Set
UMLS	Unified Medical Language System
USDA	United States Department of Agriculture
UTI	Urinary Tract Infection
VCRC	Vasculitis Clinical Research Consortium
MDCRC	Muscular Dystrophy Cooperative Research Center
WHO	World Health Organization
WIN	Weight-control Information Network

XMRV	Xenotropic murine leukemia virus-related virus
ZFNs	Zinc-finger Nucleases