

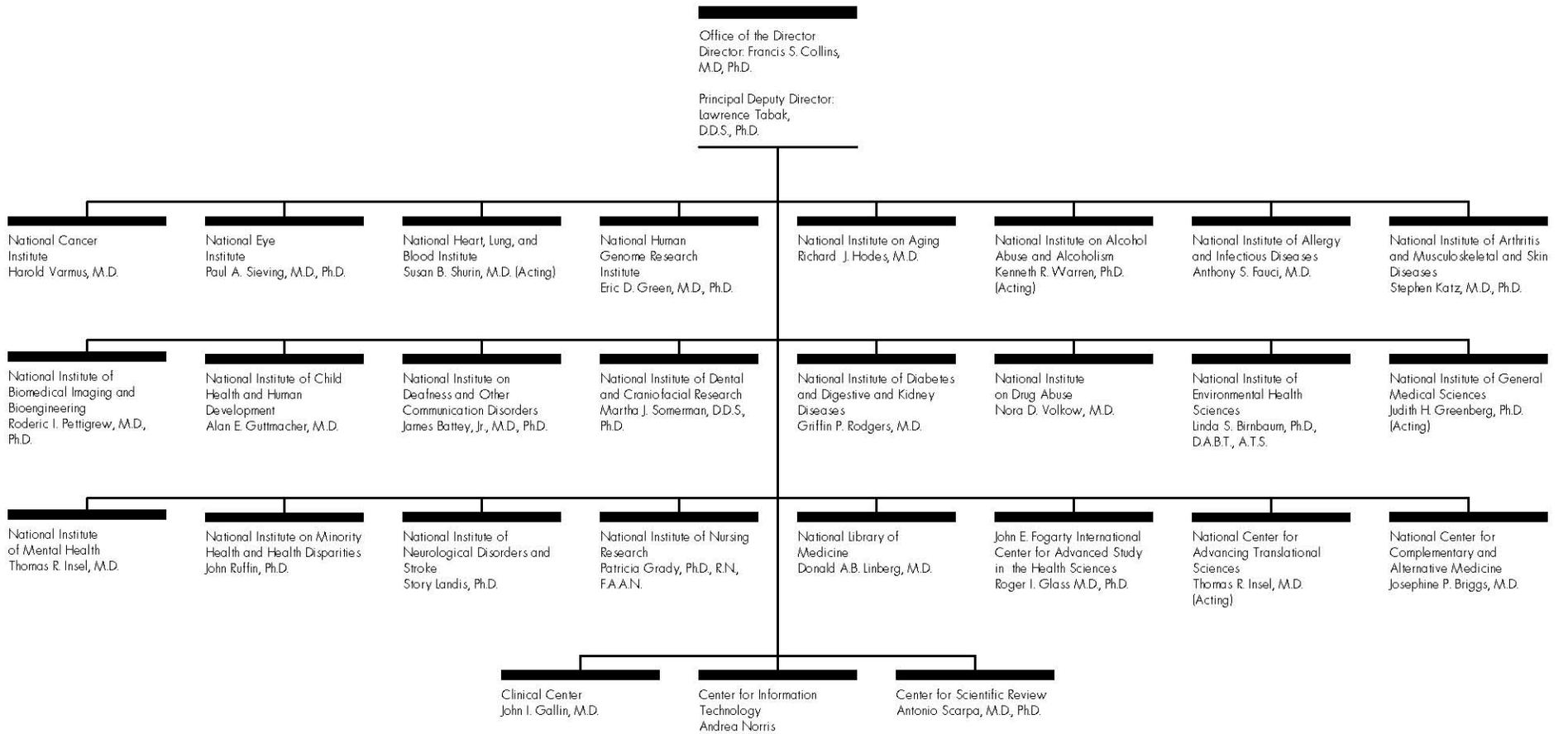
Department of Health and Human Services

National Institutes of Health

Executive Summary

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National Institutes of Health



National Institutes of Health

FY 2013 Congressional Justification

Introduction and Mission

The mission of the National Institutes of Health (NIH) is to advance fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy lives and to reduce the burdens of illness and disability. Investments in basic biomedical and behavioral research make it possible to understand the causes of disease onset and progression, design preventive interventions, develop better diagnostics, and discover new treatments and cures. Realizing the benefits of fundamental biomedical discoveries depends on the translation of that knowledge into the development of new diagnostics, therapeutics, and preventive measures to improve public health. Investments in translational research are leading to the identification of new targets and pathways for the development of new therapeutics.

The successful, ongoing pursuit of this mission also depends on a robust research enterprise that provides biomedical researchers with the tools and incentives that help foster discovery, and on the strategic deployment of a range of resources. These include state-of-the-art technologies and facilities for scientific investigation; mechanisms for data sharing and interdisciplinary collaboration; and the means to translate fundamental research findings into clinically useful applications. Basic discovery, translational research, and therapeutically promising clinical research also require well-trained scientists. Thus, NIH must also invest in the training and career development of the current and future biomedical workforce. Investments in the public good of biomedical research pay invaluable dividends—for the continued progress of science, for the sick and the well, for economic growth and U.S. competitiveness, and for society as a whole.

**National Institutes of Health
FY 2013 Congressional Justification**

**All Purpose Table
(Dollars in Thousands)**

	FY 2011 Actual ²	FY 2012 Enacted	FY 2013 President's Budget
Labor/HHS Discretionary Budget Authority	\$30,688,288	\$30,623,259	\$30,623,259
Interior Budget Authority	79,054	78,928	78,928
Total Discretionary Budget Authority	\$30,767,342	\$30,702,187	\$30,702,187
Mandatory Type 1 Diabetes Research	150,000	150,000	150,000
Total Budget Authority	\$30,917,342	\$30,852,187	\$30,852,187
NIH Program Level ¹	\$30,925,542	\$30,860,387	\$30,860,387
<i>Number of Competing RPGs</i>	8,706	8,743	9,415
<i>Total Number of RPGs</i>	36,366	35,944	35,888
<i>FTEs</i>	18,569	18,569	18,383

Note: FY 2011 and FY 2012 figures are shown on a comparability basis to FY 2013 (including the NCATS reorganization).

¹ Includes NLM Program Evaluation of \$8.2 million.

² Labor/HHS Discretionary Budget Authority includes \$998 thousand for transfer from the General Departmental Management (GMD) fund to support the Inter-agency Autism Coordinating Committee (IACC) in FY 2011. Funding for this purpose is included in the FY 2012 and FY 2013 Labor/HHS Discretionary Budget Authority Request.

**National Institutes of Health
FY 2013 Congressional Justification**

OVERVIEW OF THE BUDGET REQUEST

Total Budget Request

(Dollars in Millions)

	FY 2012 Enacted	FY 2013 President's Budget Request
Total Program Level ¹	\$30,860	\$30,860
Change from FY 2012 Enacted: Dollars	--	\$0.0
Change from FY 2012 Enacted: Percent	--	0.00%

¹ Reflects discretionary budget authority from Labor/HHS and Interior (Superfund), mandatory Type 1 Diabetes and NLM Program Evaluation funds.

The President's Budget request for the National Institutes of Health (NIH) is a total program level of \$30.860 billion for fiscal year (FY) 2013—the same overall level as FY 2012. This funding is devoted to basic and translational research aimed at maintaining a vibrant and well-trained scientific workforce to advance the nation's health and economic well-being. NIH will invest in areas of the most extraordinary promise for biomedical research and continue to support the scientific workforce, working to recruit and retain the best and brightest from all of the nation's diverse populations, to tackle the major health challenges facing the Nation now and in the future.

NIH research has an impressive track record of contributing to tangible improvements in the diagnosis, treatment, and prevention of disease, including quality-of-life enhancements and economically beneficial changes such as:

- Between 60 to 70 percent reductions in the death rates for coronary disease and stroke in the last half century;
- Effective interventions for HIV/AIDS prevention and treatment such that it is possible to imagine an AIDS-free generation;
- A nearly 30 percent decline over the last three decades in the age-standardized prevalence of chronic disability among American seniors;
- A 40 percent decline in infant mortality over 20 years and better treatments for premature and low-weight births, resulting, for example, in increased survival, prevention of cerebral palsy, and better developmental outcomes; and,

NIH Funding Generates Jobs and Economic Growth

Every dollar of NIH funding generates about \$2.21 in economic output.¹

In fiscal year 2010, NIH extramural research funding generated \$68.035 billion in new economic activity nationwide and supported more than 487,900 jobs.²

¹ *In Your Own Backyard, Families USA, June 2008.*

² *An Economic Engine, United for Medical Research, Spring 2011.*

- Over 150 new FDA-approved drugs and vaccines or new uses of existing drugs.¹

NIH research is generating discoveries at an unprecedented rate—discoveries that are opening new avenues for disease treatment and prevention, revolutionizing patient care, and generating substantial economic growth. Tomorrow’s advances in health care depend on today’s investments in research to: understand the fundamental causes and mechanisms of disease; design new technologies to accelerate these discoveries; 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. This wide breadth of research depends on having a robust pipeline of creative and skillful investigators.

This investment in the future health of all Americans has immediate benefits as it plays a key role in reinvigorating the economy. Numerous economic analyses have documented the role that NIH research plays in creating jobs and spurring economic growth. Additionally, in the face of growing global competition, sustained investment in scientific innovation and the scientific workforce in the US will continue to propel scientific discovery. Investing in innovation—the nation’s long-term engine of economic growth—affects the nation’s global competitiveness. Countries such as China and India are increasingly investing resources into biomedical science and technology. As just one example, although the U.S. led the effort to map the human genome, and a recent economic estimate suggests that this has resulted in a 141-fold U.S. return on investment,² China is moving to assume the position of world leader in genomic sequencing. With its recent purchase of 128 highly-advanced genome sequencers, the Beijing Genomics Institute alone now has more DNA sequencing capacity than all of the NIH-supported genome centers combined.

1. Investing in Basic Research

Investments in basic biomedical and behavioral research make it possible to understand the causes of disease onset and progression—an understanding that is essential to the development of better diagnostics, the design of preventive interventions, and the discovery of new treatments and cures.

¹ From: the National Long-term Care Survey; Stevens, A.J., et al. “The Role of Public-Sector Research in the Discovery of Drugs and Vaccines.” *New England Journal of Medicine* 2011;364:535-41.

² *Economic Impact of the Human Genome Project: How a \$3.8 Billion Investment Drove a \$796 Billion in Economic Impact, Created 310,000 Jobs and Launched the Genomic Revolution*, Batelle Technology Partnership Practice, May 2011.

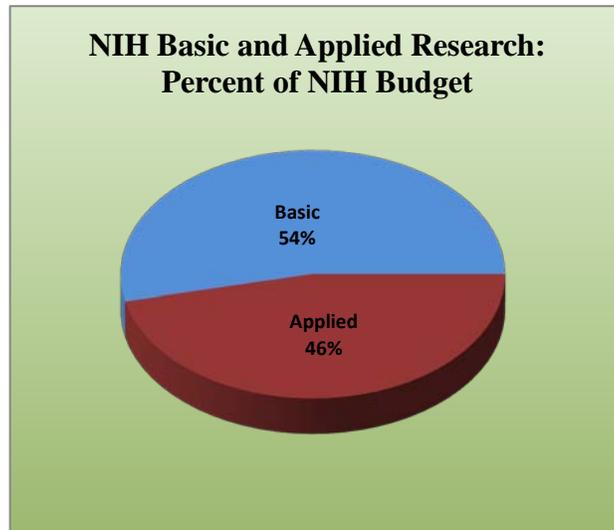
For example, basic research on the communities of bacteria and other microorganisms (the “microbiome”) that normally live in the human digestive tract has revealed that these organisms play an essential role in maintaining health by aiding digestion. Researchers have now uncovered evidence that change in the composition and activity of the microbiome contribute to the development of obesity, which has reached epidemic proportions in the U.S. It is hypothesized that the normal bacterial communities are being affected by environmental factors such as diet and antibiotic exposure, and that these changes can be passed on from mother to child. Such research offers great promise to provide novel approaches to the prevention of obesity.

Basic research discoveries that shed light on how biology works generally have broad and far reaching relevance. For example, using powerful methods derived from long-term NIH investments in structural biology, NIH researchers recently deciphered the three-dimensional structure of a key biological receptor involved in inflammation. Armed with this knowledge, scientists can now explore the intimate details of how this type of receptor is activated, offering new avenues of hope for those suffering from such diverse diseases and conditions as heart disease, arthritis and respiratory disorders.

Our knowledge of biology has become increasingly more sophisticated and integrated, in part due to dramatic technological advances that allow researchers simultaneously to study all the genes, proteins, and metabolites of a cell, tissue or organ. This approach enables investigators to discern interactions among biological pathways and to evaluate the entire spectrum of biological responses to the environment, drugs, and other extrinsic factors — so-called “systems biology.” Fueled by these new technologies, systems biology research is accelerating the pace of discovery and reducing its cost.

In addition to a rapidly expanding understanding of basic biology, new technological and methodological advances have vastly improved our ability to generate research findings that contribute to understanding environmental and behavioral influences on health. New developments in research design, data collection strategies, and analytic techniques have opened new avenues towards uncovering the effects of environmental factors ranging from, for example, air quality to family dynamics, on health and well-being.

Each year, basic science researchers make thousands of discoveries that add to our ever-increasing knowledge about biological mechanisms and processes that affect health and disease. As the chart below shows, approximately 54 percent of the NIH budget is devoted to basic research.



Genomics

One of the current priorities in NIH basic research is to capitalize further on the revolution in genome sequencing. Genetic discoveries are providing valuable insights into common biological pathways and biochemical and molecular mechanisms, insights that inform many areas of biomedicine. Genetic variants associated with disease are being identified at a stunning rate, laying the groundwork for new diagnostic tools and novel drug targets for heritable disorders, harbingers of the age of personalized medicine. Genomic discoveries already inform many medical treatment decisions. For example, breast cancer and colorectal cancer patients are now tested for gene mutations in order to guide drug choices. Likewise, genetically guided prescriptions of the anti-retroviral abacavir (Ziagen) are now the standard of care for patients with HIV. With continued progress in genomic discoveries and the technology to sequence genes, the age of personalized medicine, in which all treatments are finely tailored to the individual, is becoming closer to reality.

**The Economic Benefits of Public Investments in Biomedical Research:
The Case of Genomics**

- Through the completion of the human genome project (HGP) in 2003, the U.S. government invested \$3.8 billion.
- Between 1988 and 2010, human genome sequencing projects and associated research and industry activity, directly and indirectly, generated economic activity totaling \$796 billion, personal income exceeding \$244 billion, and 3.8 million job-years of employment.
- The government's initial investment yielded an economic return of 141 to 1.
- In 2010 alone, genomics-related economic activity yielded over \$3.7 billion in federal taxes and \$2.3 billion in state and local taxes.
- Also in 2010 alone, human genome sequencing projects and associated activity directly and indirectly generated \$67 billion in U.S. economic output and \$20 billion in personal income.

From Economic Impact of the Human Genome Project: How a \$3.8 Billion Investment Drove a \$796 Billion in Economic Impact, Created 310,000 Jobs and Launched the Genomic Revolution, Batelle Technology Partnership Practice, May 2011.

Genomics of Model Organisms

Animal models are essential to the study of human disease and the development of therapies. Research on bacteria, yeast, insects, worms, fish, rodents, primates, and even plants has shown that certain basic functions are nearly the same in all living organisms, which means that understanding biological functions in animals can shed light on such functions in humans. NIH is supporting an effort, called “modENCODE,” to illuminate the genetic control systems in two important model organisms, the fruit fly and roundworm. These genetic control systems coordinate the vast signaling networks that turn DNA “on” and “off.” Many disorders, from cancer to schizophrenia, are caused by problems in such control systems. Using advanced sequencing and computing methods, this initiative is generating extensive data that will help identify important functional elements across the genomes of these organisms. These discoveries are expected to provide potential targets for the development of therapies for human diseases.

Proteomics and Metabolomics

Basic research also is advancing our understanding of biological processes involving proteins and metabolic pathways, both of which underpin human physiology and the body’s response to external factors, including drugs.

Proteomics is the study of the structure and function of the entire set of proteins in a cell, tissue, organ, or organism. Knowing a protein's structure can provide clues about how it functions normally, how it behaves abnormally in a diseased cell, and how its function may be restored by therapeutics. Proteomics has led to the identification and development of biomarkers to detect heart damage, breast cancer subtypes, and the recurrence of thyroid cancer. Metabolomics goes a step further, focusing on the products of chemical reactions throughout the body, called metabolites. These encompass carbohydrates, lipids, and other molecules produced by our bodies, for example cholesterol levels in the blood. Metabolites also come from microbes living in our bodies and the things we eat and breathe. As the output of biological processes, metabolites are good indicators of nutrition, infection, environmental exposures, drug metabolism, and general health status. Metabolomic profiling of a broad array of tissues in a variety of disease states is helping to identify the normal and pathological roles of metabolites in biological processes.

Both proteomic and metabolomic approaches are being deployed in biomarker and discovery research to find signatures for disease diagnosis, prognosis and treatment response. To further accelerate proteomic and metabolomic discoveries, next generation technologies are needed to enhance the specificity, sensitivity, and speed of analyses. NIH is investing in efforts to develop these next generation technologies.

Stem Cell Research

NIH funds research using a variety of different types of stem cells, many types of which are pluripotent (pluripotent stem cells are capable of differentiating into all tissues of an organism, but cannot on their own sustain the full development of an organism). For example, scientists are using “induced” pluripotent stem cells (iPSCs) developed from the adult cells of patients with particular diseases. These cells display many of the key characteristics of the patient’s disease and, therefore, they offer an important model for both understanding the disease and developing and testing potential therapies. For example, cardiac cells derived from iPSCs of patients with Long QT syndrome, a disorder of the heart’s electrical system, exhibit characteristic features seen in the cardiac cells of those patients, including abnormalities in the way electrical impulses are conducted. Dopaminergic neurons derived from iPSCs from patients with a certain form of Parkinson’s disease die more readily when exposed to chemical stress. The ability to reproduce the molecular abnormalities of these diseases (and many others) in a cell culture allows discovery of new and powerful targeted therapies.

A new and very promising area of stem cell research involves reprogramming a cell directly from one type to another—known as “transdifferentiation” or “direct reprogramming.” NIH-supported scientists used this strategy in mice to convert exocrine cells that secrete digestive enzymes in the adult pancreas into endocrine cells that behaved like the insulin-secreting beta cells. NIH-funded scientists used similar techniques to convert human fibroblasts directly into functional nerve cells or cardiac muscle cells. Given these successes, scientists are now working to generalize methods for direct reprogramming. For example, investigators are exposing fibroblasts to pluripotency factors for a short time period so that they are destabilized but do not become pluripotent. The cells are then directed into specific lineages, such as neural progenitor cells, which can then be expanded to larger numbers prior to further differentiation. In contrast to iPSC-derived cells, no residual pluripotent cells are present that would have to be removed from any cell product.

Two FDA-approved clinical trials currently are underway to test cell products derived from human embryonic stem cells (hESCs) for treatment of degenerative eye diseases. Advanced Cell Technology, Inc. is conducting two trials using retinal pigment epithelial cells to treat Stargardt’s macular dystrophy and the “dry” type of age-related macular degeneration.

While progress has been made in moving pluripotent stem cells, including hESCs and iPSCs, to the clinic, advances can be accelerated through focused efforts. To this end, the NIH Center for Regenerative Medicine (NIH CRM) has been created within the NIH Intramural Research Program to serve as a national resource for stem cell science focused on facilitating the development of medical applications and cell therapies. NIH CRM’s goals are to identify the most promising projects that will take advantage of the new technologies as well as novel sources of adult stem cells and use them as pilots in the development of strategies for translation.

National Children’s Study

The National Children’s Study (NCS) is a unique longitudinal birth cohort observational study that will examine the effects of genetics and the environment--broadly defined to include factors

such as air, water, diet, family dynamics, community and cultural influences--on the growth, development, and health of children across the United States. The study will result in a wealth of data to analyze how environmental factors interact with each other and what helpful and/or harmful effects they might have on the growth, health, and development of children and ultimately adults. Findings from the study will benefit all Americans by providing researchers, health care providers, and public health officials with evidence-based information to improve health, develop prevention strategies, and health and safety guidelines, as well as to guide future research. There are two related phases of the NCS: the Vanguard Study and the Main Study. The Vanguard Study is a pilot study that is designed to provide data that inform the implementation of the Main Study. In FY 2013, the Vanguard Study will continue and activities for the Main Study will begin. By building on existing infrastructure and streamlining administrative components, in FY 2013 the NCS will be able to save significantly on costs.

2. Accelerating Discovery Through Technology

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 (i.e. to define *all* of: 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 only in the last few years, include DNA sequencing, microarray technology, nanotechnology, new imaging modalities, and computational biology.

Large-scale Sequencing Technologies

Advances in sequencing technology are essential to NIH's progress in genomics. Since the sequencing of the human genome more than ten years ago, the average cost of sequencing an entire genome has fallen from more than \$100 million to about \$10,000, and will continue to drop as NIH-supported large-scale DNA sequencing centers implement emerging technologies to achieve the highest efficiency of DNA sequencing. In time, whole genome sequencing will be routinely used by clinicians to improve the prevention, diagnosis, and treatment of human disease. Bringing the fully loaded cost of genome sequencing to under \$1,000 within this coming year, now promised by two companies, is likely to lead to tremendous changes in how clinicians diagnose and treat disease, and it will enable researchers to make even more rapid and efficient progress in developing new diagnostic, treatment and prevention tools.

NIH also is supporting the development of a rapid real-time technology that detects genomic sequences with new electronic technology that avoids many of the time-consuming steps and expenses that are characteristic of most of the current systems. This technology has great potential to increase the efficiency and speed of whole genome sequencing, while also lowering its cost to far below \$1,000 using systems that would be simple to deploy in clinical laboratories.

Advanced gene sequencing technologies also have opened up new, more efficient avenues of targeted gene discovery efforts. These techniques allow investigators to hone in on the genetic mutations that underlie the pathogenesis of many heritable diseases. These targeted approaches have already led to the identification of the causes of certain rare diseases and are laying the groundwork for the discovery of disease biomarkers and the development of targeted interventions and therapeutics across many diseases and disorders.

The Cancer Genome Atlas

One of NIH's highest current priorities is The Cancer Genome Atlas (TCGA), a project to generate comprehensive, multi-dimensional maps of the key genomic changes in major types and subtypes of cancer. There are hundreds of different types of cancer, each caused by glitches in DNA that trigger the uncontrolled growth of cells. Identifying the genetic changes that are associated with different types of cancers and understanding how such changes drive the disease process will lay the foundation for a personalized era of cancer care that will improve patient outcomes.

TCGA is a powerful resource for a new generation of research aimed at developing better strategies for diagnosing, treating, and preventing each type of cancer. Jointly led by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), and with its timetable substantially accelerated by American Recovery and Reinvestment Act (ARRA) funds, TCGA is charting the complex pathways involved in more than 20 types of cancer. This pioneering effort to map systematically and analyze cancer genomes on a large-scale basis ultimately will change the way cancer is treated and should significantly shorten the time and reduce the costs involved in drug development.

Recent TCGA discoveries include:

- TCGA characterized the molecular aberrations that cause ovarian cancer, the fifth-leading cause of cancer death among women. One astonishing finding was that 96 percent of tumors contained mutations in a single gene known as TP53.
- Acute myeloid leukemia (AML) is an aggressive blood cancer that kills 9,000 Americans annually. TCGA researchers recently reported the discovery of mutations in a single gene that appear responsible for treatment failure in a significant number of AML patients. The finding should prove useful in treating AML patients and may provide a molecular target for developing new drugs.

Technologies for Systems Biology

Other exciting opportunities to gather comprehensive information in systems biology have recently emerged. As mentioned above, one such opportunity is metabolomics – the ability to measure cellular levels of sugars, lipids, amino acids, nucleotides, and ions sensitively and cost-effectively, and to see how these metabolites are altered in the presence of disease. The field of proteomics (i.e. measurement and functional assessment of all the proteins in a tissue or cell type), also mentioned above, is poised to move into a new and more comprehensive mode, if

appropriate resources are invested in technology development. These advances in systems biology will be particularly powerful if the technology is advanced to the point where measurements can be reliably made on single cells.

Understanding environmental contributions to health and disease has never been more important, but current technologies only detect a small fraction of the substances whose impact may be important to understand. Thus, the development and deployment of sensitive technologies to assess potential toxins in the air, water, and food are high priorities. New engineering approaches, aided by real time cell phone transmission, make major advances possible.

The development of new molecular imaging techniques has arrived at an important juncture to develop new positron emission tomography (PET) ligands, further advances in magnetic resonance imaging (MRI) scanning resolution, more accurate ultrasound methods for vascular assessment, and new methods with high sensitivity and specificity to detect the presence of diseases like prostate cancer at the earliest possible moment.

Technologies for the Earlier Detection of Cancer

Early detection of cancer is critical to provide effective therapy. Supported through the National Institute of Biomedical Imaging and Bioengineering, investigators recently reported the detection of *a single metastatic cell* from lung cancer in one billion normal blood cells. These circulating tumor cells (CTCs) may also be released into the bloodstream of patients with invasive but localized cancers. The presence of CTCs may be an early indicator of tumor invasion into the bloodstream long before distant metastases are detected. Identifying CTCs may be viewed as performing liquid biopsies, which can be especially advantageous for prostate cancer. Researchers plan to extend their work to develop a point-of-care microchip that would allow non-invasive isolation of CTCs from patients with many different types of cancer, to improve the management and treatment of this devastating disease.

Through this investment in technologies for discovery, NIH will support the development and application of state-of-the-art technologies including computational biology, proteomics, genomics, metabolomics, single cell biology, stem cell biology, environmental technology, and new imaging technologies.

3. Advancing Translational Sciences

Realizing the benefits of fundamental biomedical discoveries depends on the translation of that knowledge into the development of new diagnostics, therapeutics, and preventive measures to improve public health as well as the widespread adoption of those measures so that all may benefit. 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 wide door of opportunity in translational science. Yet, today,

the process of translating fundamental knowledge into new or better clinical applications is an exceedingly complex, costly, and risk-laden endeavor. The need for innovative strategies for therapeutics development is now widely recognized throughout the biomedical research community. In addition, this is a time when technology allows for rapid, widespread communication to all, including the communication of scientific and clinical breakthroughs. Yet, simply communicating scientific breakthroughs and the availability of new treatments does not assure that they will be adopted in common medical practice. New partnerships are needed with all sectors involved in healthcare to allow for rapid dissemination and adoption of new treatments so that they will be applied to all those who need them.

NIH currently is pursuing efforts to streamline and shorten the pathway from discovery to health and is well positioned to support these activities in substantial ways. This expectation is grounded in several recent developments. These include the dramatic acceleration in understanding the molecular basis of hundreds of diseases; the establishment of the National Center for Advancing Translational Sciences (NCATS); the forging of public-private partnerships to aid the movement of drug candidates identified by academic researchers into the commercial development pipeline; and the creation of a network of healthcare delivery organizations to conduct research that will hasten the translation of research results to ‘real world’ health practice. In 2013, NIH will continue to build on existing efforts, pursue exciting new opportunities, and forge new partnerships to accelerate progress in translational science.

National Center for Advancing Translational Sciences (NCATS)

Established in FY 2012, the mission of the National Center for Advancing Translational Sciences (NCATS) is to support rigorous scientific research designed to reengineer elements of the development pipeline that moves basic research findings into new diagnostics and therapeutics. With a specific focus on the process for translating scientific discoveries into better identification and treatment of disease, NCATS seeks to catalyze the generation of innovative methods and technologies that may be applied to efforts across a wide range of human diseases and conditions. Rather than focusing on specific diseases or conditions, NCATS-supported projects focus on addressing scientific and technical challenges to reduce, remove, or bypass significant bottlenecks across the continuum of translation. NCATS also ensures that results, both positive and negative, are shared in an open and collaborative environment. In this way, NCATS provides other NIH Institutes and Centers, as well as the private sector, the tools, methodology and infrastructure to speed the development of new therapeutic approaches.

Given this mission, NCATS is central to NIH’s efforts to forge new partnerships between the pharmaceutical industry, government, academia, and the non-profit sector. For example, its advisory structure is unique in that it includes representation from a wide range of disease advocacy organizations, private equity firms, and scientific expertise from a number of disciplines within translational science and regulatory review. Within NCATS, the NIH Clinical and Translational Science Awards (CTSA) program enables the creation of innovative research teams including all sectors of healthcare to address complex health and research challenges in clinical research. To explore other critical translational areas and innovative public-private sector partnership models, NCATS will be working with other NIH Institutes and Centers to convene workshops with industry, venture capital, other research funders, and non-profits as well as the

Food and Drug Administration and the U.S. Patent and Trademark Office. For example, in FY 2012, NCATS will bring these stakeholders together to explore new models to advance medical device innovation and new models for commercializing research on new indications for compounds at or near the end of their patent life.

Target Validation

By capitalizing on dramatic scientific advances in genomics, investigators now understand, at the molecular level, the basis for thousands of diseases, both common and rare. With this understanding, researchers can identify new molecular targets, and better validate targets currently under investigation, for therapeutic potentials. But there is almost an embarrassment of riches in this outpouring of new discoveries, and powerful new and creative methods are needed to mine and analyze the wealth of genomic information available to better predict which enzymes, proteins, receptors, pathways, etc. are most likely to be clinically relevant targets for therapeutics. Earlier and more accurate identification and validation of drug targets can increase the likelihood of success and reduce costs associated with drug development. Currently, the failure rate during Phase II clinical trials—the first time a drug candidate is tested for efficacy in humans—is more than 80 percent, with about half of the failure due to a lack of benefit for the disease being studied.³

NIH has a number of programs underway to collect and analyze genomic and related data and to develop the tools and infrastructure necessary to mine it for the most promising drug targets. Two such programs are:

- The *Genotype-Tissue Expression (GTEx)* program, part of the NIH Common Fund, which studies human gene expression and regulation in multiple tissues. The ultimate goal is to develop a database that correlates patterns of gene expression with genotypes, providing valuable insights in gene regulation and disease-related perturbations.
- The *Library of Integrated Network-based Cellular Signatures (LINCS)*, also a Common Fund program, which is collecting, organizing, and analyzing a wealth of information to better understand how various biological pathways interact and how they change or respond to genetic and environmental stressors, or to drugs.

The unprecedented challenges of developing new drugs based on the enormous volume and unique nature of molecular information available today also pose an unprecedented opportunity for increased sharing and collaboration. NIH is actively involved in a joint program with industry partners to accelerate and streamline the process of validation of potential drug targets. Under the old model of drug development, organizations worked in isolation and essentially “recreated the wheel” in parallel, collecting similar types of data and different internal mechanisms to validate potential targets.

Through growing partnerships—with NIH providing information and expertise, but also playing a unique, convening role—the biomedical community now is developing the infrastructure to

³ Arrowsmith J. “Trial watch: Phase II failures: 2008-2010.” *Nature Reviews Drug Discovery* 10, 328-329 (May 2011) | doi:10.1038/nrd3439

share data and the knowledge across sectors and developing approaches to use this data to better identify and evaluate promising targets. Industry leaders now agree that target validation of this sort is pre-competitive information. This not only reduces redundancy and saves resources, but the combination of shared data and expertise also results in a more thorough and powerful toolkit to facilitate target validation efforts.

Predictive Toxicology

More effective and efficient approaches to assess the relative safety of potential therapeutic compounds for use in humans would contribute to accelerating the development of new techniques. While the current preclinical regulatory system is built largely around safety studies in animals, it is clear that these models often fail to predict human risk accurately. New and promising approaches using human-based cellular systems and high throughput screening (HTS) have been developed and work is underway to validate the predictive power of these new systems. For example, through the Tox21 Program (“Toxicology in the 21st Century”), NIH supports an ongoing collaboration among the NIH Chemical Genomics Center, the NIH National Toxicology Program, the Environmental Protection Agency, and the Food and Drug Administration. The Tox21 Program uses the NCGC's high-speed, automated screening robots to test thousands of potentially toxic compounds. Over 10,000 drugs and chemicals are being tested across hundreds of biological assays to assess effects on every pathway operating in mammalian cells.

NIH is also collaborating with FDA and the Defense Advanced Research Projects Agency (DARPA) on a bold initiative to foster the development of improved model systems to predict efficacy, safety, bioavailability, and toxicology outcomes for candidate therapeutics. NIH and DARPA, in consultation with FDA, both released requests for projects that aim to develop systems of human physiology, such as using three dimensional tissue blocks derived from iPS cells, that are more representative than current models, such as animal models, and that can be used to better predict the safety of new drugs and biologics in humans.

Advances in high throughput platforms coupled with collaborations and the sharing of analytical tools and information on databases are expected to revolutionize the development of therapeutic products. In addition to generating information that is more predictive of the safety of compounds in humans, these new approaches to toxicology screening may also have the additional benefit of reducing, or even replacing the use of animals in toxicity testing.

Rescue and Repurposing

Drug rescue and repurposing research is another area where NIH is focusing efforts to accelerate progress. All approved drugs and many abandoned compounds have been tested in humans, and have detailed, associated information regarding dosing, pharmacology, and toxicity. Rescue and repurposing provide opportunities to leverage previous research and development efforts to develop new drugs more rapidly. Drug “rescue” refers to research on previously abandoned compounds (that is, compounds on which earlier research, development, or approval was stopped for one reason or another), whereas “repurposing” refers to research on approved drugs for new indications. For example, in the early days of the AIDS epidemic, NIH investigators

collaborated with academic and industry experts to rescue Azidothymidine (AZT) —a compound that was initially investigated for use in cancer, but was abandoned because it was not effective in animal models. Similarly, drugs that have been approved for one disease or indication may also prove to be effective for other conditions as well. Hydroxyurea, initially approved for use in cancer, subsequently was repurposed by investigators at NIH as a treatment for sickle-cell anemia.

NIH recently launched an initiative on rescue and repurposing that will have a home in NCATS. NCATS will address the critical elements of visibility—providing a portal through which outside investigators can learn about and access resources and expertise; clearinghouse—accepting and organizing abandoned compounds and associated data so they can be made available for rescue and repurposing; and matchmaking—identifying and facilitating potential partnerships. NCATS also will curate the *NIH Chemical Genomics Center* (NCGC) Pharmaceutical Collection (NPC). The NPC is a one-of-a-kind, comprehensive, publicly-accessible collection of approved and investigational drugs—an essential resource providing the foundation for rescue and repurposing. The agency is continuing to confer with industry, academia, and FDA to identify new opportunities in rescue and repurposing, including discussion with industry collaborators on providing academic investigators access to abandoned compounds and NIH funding to pursue new indications.

Neurotherapeutics

Disorders of the nervous system such as Alzheimer’s Disease, Parkinson’s Disease, depression, schizophrenia, hearing loss, and other conditions specific to the nervous system- affect tens of millions of americans. But the process for developing new treatments for these disorders is costly and has a high likelihood of failure given the complexities of the brain. Basic neuroscience researchers often lack the resources to develop their findings further into novel therapeutic strategies where they can attract the interest of industry. Biopharmaceutical companies often hesitate to invest in neurotherapeutics development because there are few clinically validated targets or strategies. In order to bridge this seeming divide, NIH has created the Blueprint Neurotherapeutics Network. Project teams supported by this network receive support for their research along with access to an infrastructure that is normally only available to biopharmaceutical companies. Pharmaceutical and biotechnology industry consultants assist investigators throughout the treatment development process, from chemical optimization, to biological testing, to early-stage clinical trials. Currently underway through this network are projects to develop new treatments for Alzheimer’s Disease, macular degeneration, depression, Amyotrophic lateral sclerosis (ALS or Lou Gehrig’s Disease), among others, with plans to fund up to 20 projects in the coming years.

Innovations in Clinical Trial Design

NIH supports studies related to all aspects of clinical trials, including studies that involve innovations in trial design. The goals of innovation in clinical trial design are to perform trials faster, more efficiently, more effectively, and with the fewest number of subjects needed for determining the intervention’s safety and effectiveness. Optimized clinical trials will result not only in reduced costs and administrative burdens, but also in fewer study subjects put at risk of

potential harm. The need for innovative clinical trial designs would be particularly beneficial for advancing treatments for rare and pediatric diseases.

Thanks in large part to insights from the sequencing of the human genome, researchers now recognize that there may be many different forms of a given disease, and they are designing trials in a more rational way by using genotyping to assist in subject selection. In addition to using genomic signatures and other technologies to improve trial design, NIH plans to continue its efforts to help identify new and improved biomarkers and other outcome assessment measures, such as patient- or clinician-reported outcome measures, to be used as primary and secondary endpoints in trials.

Another emerging approach to clinical trial design involves looking anew at the goals and methods of early stage clinical trials in order to maximize the information gained. Traditionally, first-in-man, exploratory, and phase I trials only assess safety; however, these trials also can provide some information on effectiveness. Given that the majority of trials fail in phase II and the enormous expense of failures at that stage, it is imperative that NIH help the field to rethink the assessment of efficacy in early phase studies. Thinking “anew” also involves taking new information and applying it to future drug development programs. For instance, combination therapies, which aim at more than one target, show the most promise for treating certain diseases or conditions such as HIV and cancer. NIH, along with its partners such as the FDA, must take a leadership role and help to develop the science base to guide the appropriate clinical trial designs when using drugs in combinations.

Selected Examples of High Priority Clinical Trials

NIH also supports the conduct of clinical trials for the development of new treatments for many diseases and conditions. The following are examples of clinical trials that offer great promise:

- Universal Influenza Vaccines. Seasonal flu outbreaks are an unfortunate hallmark of the late fall and winter. The flu sweeps through communities, creating an epidemic that affects up to one in five Americans. While most get better within a week, for some, the flu and its complications can be life-threatening. Each year in the U.S., seasonal influenza kills more than 36,000 people and hospitalizes 200,000 more, even with the widespread use of annual, seasonal flu vaccines. In addition to the annual risks, the looming risk of a worldwide pandemic of a new influenza strain, such as the H1N1 threat from 2009-10, or the avian H5N1 strain that could break out at any time, threatens the world’s ability to prepare.

The ultimate goal for flu vaccine researchers is to develop a universal vaccine—one that protects against multiple strains of influenza for extended periods of time, potentially extending periods between vaccinations to several years.

NIH research offers optimism for a universal flu vaccine. Three different clinical trials, all using two-step (prime-boost) vaccination strategies are ongoing or planned.

- HIV/AIDS. Despite significant strides in the treatment and prevention of HIV infection and AIDS, more than 33 million people worldwide are infected with HIV, with approximately 7,000 new infections occurring daily. In the U.S., approximately 56,000 people are infected with HIV annually. Thus, a vaccine and other approaches to preventing infection are a top priority for NIH.

Encouraged by the partial success of an HIV vaccine in the recent Thailand trial, NIH is undertaking a study to evaluate the ability of a related vaccine to prevent HIV infection and reduce viral replication in subjects who receive the vaccine but later become infected with HIV. The study is to enroll at least 2,200 subjects at 21 U.S. sites in 18 cities.

Microbicides are another important prevention approach. An effective microbicide regimen could prevent transmission of HIV to women through sexual intercourse with an infected male partner. Yet, so far no microbicide product has been approved for use outside of research studies. An ongoing NIH study is evaluating the safety and effectiveness of three different tenofovir-based microbicide regimens. A planned phase III trial would assess the safety and effectiveness of administering an experimental antiretroviral drug, dapivirine, and would be the first large efficacy study to evaluate a different delivery method for an antiretroviral-based microbicide product.

In a dramatic recent study, NIH research has demonstrated that early treatment of an HIV-infected individual can reduce the risk of sexual transmission of HIV to an uninfected partner by 96%. About 60% of new cases of HIV in the U.S. are transmitted by individuals who do not know they are infected. Now NIH plans to explore whether a community-wide, voluntary “test-and-treat” strategy can prevent new cases of HIV infection. This advance, combined with other approaches to the prevention and treatment of HIV, has allowed us to begin to imagine an AIDS-free generation.

- Melanoma. Each year, more than 68,000 Americans are diagnosed with melanoma and another 48,000 are diagnosed with an early form of the disease. Despite progress in understanding the cause and prevention of this deadly form of skin cancer, nearly one American dies of melanoma every hour.

NIH is undertaking several high priority melanoma clinical trials. One is an innovative phase II trial that uses a personalized approach to melanoma therapy based on tumor genotype and prior therapy. Another is a phase III trial that targets melanoma patients who, despite prior surgery, face a high and unacceptable risk of recurrence and death. This is a timely study comparing the efficacy of two adjuvant regimens—an old established drug (interferon) with a recently approved drug (ipilimumab)—as well as quality of life with each drug. A third trial will test a combination of two different types of monoclonal antibodies.

- Cardiovascular Disease. Heart disease is the leading cause of death in the U.S. In 2007, 34 percent of all deaths were due to heart disease. The estimated economic cost for 2007 was \$286 billion—\$167 billion in direct health expenditures and \$119 billion in the indirect cost of mortality. Although these statistics paint a bleak picture, there has been

progress in treatment and prevention. For example, the death rate for heart disease peaked in 1968. Since then, the trend has been downward. In 2007, for the first time, the rate was below the all-time low in 1900. This improvement is based upon implementation of research findings supported by NIH.

NIH is continuing efforts to develop new ways to diagnose, treat, and prevent heart disease. One high priority planned clinical trial is called ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches). This eight-year comparative effectiveness trial will answer an important practical management question for the very large population of patients with stable ischemic heart disease—whether an invasive approach in combination with medical therapy is superior to medical therapy alone.

Based on many years of basic investigations largely funded by NIH, inflammation is now recognized as a major contributor to cardiovascular disease, and inflammatory biomarkers are in clinical use. However, no randomized trial has specifically addressed whether reducing inflammation can reduce heart disease risk. NIH plans to directly test whether inflammation is responsible for acute heart attack due to rupture of plaque in persons with a prior history of heart attack. The trial also will investigate whether anti-inflammatory therapy improves cardiovascular outcomes.

These are just a few examples of ongoing and planned clinical trials that will pave the way for novel treatments, diagnostics, and preventive measures that have the potential to save lives, improve quality of life and productivity, and reduce healthcare expenditures.

Advancing Clinical Research by Partnering with Healthcare Delivery Organizations

In order for new diagnostics, treatments and preventive approaches to have an impact on public health, they must be integrated into common practice. And in order for this integration to occur, these new approaches should be developed with an eye towards “real world” considerations, such as, for example, cost and training. Health care delivery organizations are critical partners in determining the real world value of new interventions. By conducting research within actual health care delivery settings, studies may provide crucial information that can change practice more immediately. In addition, the research will benefit by having access to the immense resources that healthcare delivery organizations offer, such as, for example, 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.

For example, the Dental Practice Based Research Networks (PBRNs) were established in 2005 to provide scientific evidence to guide dentists in their everyday treatment choices. 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 that are changing the way dentistry is practiced.

A new initiative of the NIH Common Fund, the Health Care Systems Research Collaboratory, will build on these kinds of investments to create a large infrastructure that will leverage the resources of healthcare delivery organizations to implement pragmatic research studies in real world health care delivery settings. This program will develop networks of Health Care Delivery Systems (HCS) in which legal issues, patient consents, and IT infrastructure are harmonized so that clinical studies requiring large patient populations may be conducted more easily. These HCS Collaboratories will conduct demonstration projects to work through the networking challenges of combining their patient populations, and they will develop connections with the Clinical and Translational Science Awards network so that the clinical research community can access the HCS Collaboratories for future studies.

4. Encouraging New Investigators and New Ideas

NIH research programs are only as productive as the scientists they support. The focus, level of creativity, and value of scientific output correlates directly with the skills and ingenuity of the people NIH employs and funds. Since its inception, NIH has sought to support and ensure the development and continuation of a vibrant, skilled scientific workforce by attracting and retaining the most talented individuals. Like all aspects of the scientific enterprise, however, these are challenging endeavors that are subject to an array of forces, some that are beyond the agency's control. For example, the growth rate in faculty-level academic positions in the biomedical sciences has slowed, constraining the employment opportunities for today's and tomorrow's trainees. Moreover, the path from student to independent investigator is, by any measure, an exceedingly long one, which constitutes a problem for both individuals and institutions.

NIH is addressing workforce and training challenges through both award mechanisms and policies, and there is evidence that NIH supported programs are helping to address some of these challenges. For example, at the graduate level, participation in a formal NIH training program is correlated with shorter times to degree and with a more productive career in terms of NIH research grant awards, publications, and citations when compared to other graduate students who complete their training at the same time in similar fields. NIH also is engaging in an ongoing, systematic process of analyzing workforce and training needs to institute new, more effective mechanisms and policies. A working group of the Director's Advisory Committee has been charged with undertaking a systematic examination of the factors that shape the biomedical workforce and developing one or more models to guide decisions that will enhance the biomedical workforce in the 21st century.

To incentivize young investigators, to support their work in discovery and innovation, and to speed their transit from student to independent researcher, NIH funds several noteworthy award mechanisms and has developed specific funding policies. For example, in order to facilitate the transition from trainee to independent investigator, NIH created the *NIH Directors' Early Independence Award* and the *Pathway to Independence Award*, both designed to move talented young scientists quickly from graduate and postdoctoral training to principal investigator status. Another program, the *NIH Director's New Innovator Award*, seeks to support research projects from exceptionally creative new investigators with the potential for unusually high scientific impact. Within the NIH Intramural Program, the new *Lasker Clinical Research Scholars*

Program supports exceptional clinical researchers who show great promise as productive independent scientists within the Intramural Program. In terms of policy remedies, NIH identifies research grant applications from early stage investigators (applicants within ten years of their terminal degree or residency training) and then equalizes the funding success of these applications with the success of applications submitted by established investigators. Although NIH has made a considerable investment in recruiting members of underrepresented racial and ethnic groups, women, individuals with disabilities, and individuals from disadvantaged backgrounds into biomedical research, much more must be done. NIH's current approaches have not gone far enough to facilitate and encourage the recruitment and advancement of underrepresented minorities in biomedical and behavioral research; thus, biomedical research is missing critical contributors from among Hispanics, African-Americans, and Native Americans. NIH must identify more effective approaches that encourage more underrepresented minorities to earn advanced degrees in the biomedical sciences and to pursue appropriate postdoctoral training.

A recent study,⁴ commissioned by NIH, has documented another issue that is in need of focused attention—namely, that black applicants for their first NIH R01 award have a substantially lower likelihood of receiving an award, even after correction for known correlative factors. The NIH Director and Principal Deputy have outlined a series of steps that will be taken to seek out the causes of this troubling discrepancy, and to mount interventions to correct it.⁵ That includes providing opportunities for junior faculty from diverse groups to participate in peer review panels, encouraging more effective mentoring, and investigating the possibility of unconscious bias in the review process. A working group of the Director's Advisory Committee has been formed to identify innovative solutions to barriers in career advancement for individuals from underrepresented racial and ethnic groups. An internal diversity task force, composed of NIH senior leadership, is systematically examining NIH intramural and extramural programs and policies related to workforce diversity.

NIH is also undertaking an evaluation of current training programs to see what is and is not working. Programs that have failed to produce results will be restructured, reinvigorated to better achieve their goals, or phased out. Those that have been successful will be nurtured and continued. NIH also will apply the lessons learned from several new research programs, including the NIH Director's Pathfinder Award to Promote Diversity in the Scientific Workforce, the trans-NIH Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering, and the National Institute of General Medical Sciences awards for Research to Understand and Inform Interventions that Promote the Research Careers of Students in Biomedical and Behavioral Sciences.

⁴ Ginther, D.K., et al. "Race, Ethnicity, and NIH Research Awards." *Science* 333, 1015-1019 (August 2011) DOI: 10.1126/science.1196783.

⁵ Tabak, L.A. and Collins, F.S. "Weaving a Richer Tapestry in Biomedical Science." *Science* 333, 940-941 (August 2011) DOI: 10.1126/science.1211704.

The NIH mission only can be achieved if the best and brightest biomedical researchers are recruited and retained in the workforce without bias regarding race, ethnicity, gender, disability, and socioeconomic background. NIH has a responsibility to set a strong example for all biomedical research organizations, and is committed to making significant progress toward this critical goal.

Alzheimer's Disease

By supporting research all along the translational continuum, from basic discoveries to the widespread use of new diagnostics, therapeutics, and preventive measures, NIH will fulfill its mission to improve public health by successfully preventing and treating a number of diseases and disorders. One such disease with devastating consequences is Alzheimer's Disease (AD). With over 40 years of NIH support for a broad and intense research program along this continuum of research, we may be on the cusp of bringing the extraordinary promise of new technologies and scientific insight to bear on understanding the causes of AD and translating this understanding into effective new diagnostics and treatment.

As part of the National Plan to Address Alzheimer's Disease, in FY 2013, NIH will support studies designed to: gain a greater understanding of the risk factors that predispose someone to the disease, identify new strategies for interrupting the disease process and test those strategies in individuals long before they show signs of this devastating disease. Recently, emerging technologies have allowed a much more comprehensive assessment of the molecular basis of the disease. Researchers can now scan the entire DNA instruction book to look for hereditary factors, and use new induced pluripotent stem (iPS) cell methods to obtain insights into the cellular processes that go awry in Alzheimer brain cells. Cutting-edge methods now allow us to "see" Alzheimer's-related changes in the living brain well before memory loss is evident, and to identify biomarkers of the disease process.

Based on this new knowledge, Alzheimer's research is poised for great discoveries. The portfolio of new research being proposed for FY 2013 will make a difference in key areas, including:

- Accelerate identification of gene variants that play a role in the disease – As described above, profound drops in the cost of DNA sequencing make it possible to analyze the complete genomes of large numbers of individuals who have known genetic risk factors for AD but who do not have the disease, or those who develop the disease but who do not have known genetic risk factors. The identification of new genes that either increase risk of AD or are protective will enhance the ability to identify new targets for treatment.
- Provide new cellular models of AD –The development of human cell-based models expressing Alzheimer's molecular traits will make it possible to conduct rapid screens of libraries of hundreds of thousands of molecules for their potential as therapeutic agents. The results of these studies will open an entirely new window in targeted therapy.
- Speed up testing of therapies in individuals at the highest risk for the disease – Though our goals are nothing short of eliminating the disease, even a five year delay in onset of Alzheimer's would provide enormous benefit. Current interventions such as intranasal insulin have shown promise of slowing progression, and will be tested in larger trials.

Together, these approaches, which range from very basic studies to clinical trials, will provide a significant boost to progress in understanding Alzheimer's disease, and will speed the development of successful prevention and treatment.

Economic Impact of NIH Research

As the primary source of training support for aspiring biomedical scientists in the U.S., NIH-funded programs make it possible, at any one time, for approximately 17,000 graduate students and post-doctoral scientists to embark on careers in academia, pharmaceutical and biotech companies, Federal laboratories, and other research institutions. The agency's career development programs support approximately 4,000 faculty-level investigators, many of whom are working toward the goal of functioning as independent researchers. (NIH provides workforce and training support through dedicated, targeted trainee and career development programs and through NIH grants.)

These statistics, however, do little to convey the broader economic benefits of NIH workforce and training investments. To grasp the economic impact of these investments, it is important to begin with the fact that the lion's share of NIH funding—84 percent—is awarded to the finest universities, institutes, and small businesses in a rigorous process of peer review. Through this process, NIH funds flow to every state and almost every Congressional district. In 2007, according to conservative estimates by Families USA, these funds (which in that year totaled \$22.8 billion) resulted in a total of 351,000 new jobs created and/or supported—including research staff directly funded by NIH grants and contracts and, through multiplier effects, persons hired as a result of additional, induced business activity.⁶ These 351,000 jobs paid an average annual wage of \$52,000 and accounted for more than \$18 billion in wages in FY 2007. According to a more recent study by United for Medical Research, in 2010, NIH directly and indirectly supported nearly 488,000 jobs and produced \$68 billion in new economic activity.⁷

Similar direct economic benefits and the “ripple-effect” value of NIH funding were identified in a study of California (as well as other states) by noted economist Everett Ehrlich, working on behalf of United for Medical Research⁷. California is first among the 50 states in terms of NIH awards and in the number of jobs made possible by those awards. In 2010, California-based institutions received \$3.3 billion in NIH grants—grants that employed an estimated 71,633 people. In fact, California is the leading state for life science research, with more than 2,200 biomedical companies and an environment conducive to public-private sector collaboration and innovation.

NIH's efforts to train, develop, and sustain a diverse, productive workforce in the biomedical sciences have implications far beyond the economic health of California and other states. These efforts are pivotal for the Nation's global competitive stature. Workforce and training investments are components in the “engine of innovation” that keeps the U.S. in the position of

⁶ Families USA. (2008). *In Your Own Backyard: How NIH Funding Helps Your State's Economy*. Washington, DC. Retrieved December, 2008 from <http://www.familiesusa.org/issues/global-health/publications/in-your-own-backyard.html>

⁷ Ehrlich, E. (2011). United for Medical Research from http://www.unitedformedicalresearch.com/wp-content/uploads/2011/05/UMR_Economic-Engine.pdf

worldwide leader in biomedical research. A steady focus on training and career development has helped to make many of the fruits of NIH sponsored research (e.g., genomic sequencing, neurotransmitters, monoclonal antibodies, therapies for cardiovascular and HIV disease) possible. A continued commitment to training and career development will enable the U.S. to maintain its global lead in biomedical innovation.

Impact on the Biomedical Research Enterprise

For FY 2013, NIH requests a program level of \$30.860 billion, which is flat from the FY 2012 Enacted level. NIH will invest in areas of the most extraordinary promise for biomedical research and continue to support the scientific workforce, working to recruit and retain the best and brightest from all of our nation's diverse populations, to tackle the major health challenges facing the Nation in the future. The request preserves NIH's highest priority activities within overall budgetary constraints.

Impact of Budget Level on Performance

(Dollars in Millions, except where noted)

Program and Measures	FY 2012 Enacted	FY 2013 PB	FY 2013 +/- FY 2012 Enacted
Research Project Grants	\$16,489	\$16,463	-0.2%
Noncompeting Inflation Rate	--	--	--
Competing Average Cost (\$ in thousands)	\$423	\$431	1.8%
Number of Competing Awards (whole number)	8,743	9,415	7.7%
Estimated Competing RPG Success Rate	18.0%	19.0%	5.6%
Research Centers	\$3,031	\$2,966	-2.1%
Other Research	\$1,833	\$1,823	-0.5%
Training Programs	\$778	\$775	-0.4%
Training Stipend Rate	2%	2%	0.0%
Research & Development Contracts	\$2,968	\$3,076	3.6%
Intramural Research	\$3,399	\$3,420	0.6%
Research Management and Support	\$1,533	\$1,535	0.1%
<i>Common Fund (non-add)</i>	\$545	\$545	0.0%
Buildings and Facilities Appropriation	\$125	\$125	0.0%
Other Mechanisms ¹	\$703	\$675	-4.0%
Total, Program Level ²	\$30,860	\$30,860	0.0%

¹ Includes Office of the Director-other, Facilities funds for NCI-Frederick, Interior Superfund Appropriation, and National Library of Medicine (NLM) Program Evaluation.

² Includes Labor/HHS Budget Authority, Interior Superfund Appropriation, Type 1 Diabetes Appropriation and NLM Program Evaluation.

Funding for Research Project Grants (RPGs), including competing and non-competing grants, will decline by 0.2 percent compared to FY 2012. The average cost of new or competing RPGs is estimated to increase by 1.8 percent. This reflects average cost comparison for competing RPGs for the National Institute of Allergy and Infectious Diseases (NIAID), which is affected by the large average cost of HIV/AIDS Clinical Trials Networks included in the FY 2013 competing RPG pool. There is an overall reduction of one percent in the average cost of FY 2013 competing RPGs, when compared to the FY 2012 competing RPG pool after adjusting for the HIV/AIDS Clinical Trials Networks. The number of new or competing RPGs would increase by 672, resulting in an estimate success rate of 19 percent.

Support for the training mechanism would decline by 0.4 percent compared to FY 2012. This reflects a 1.8 percent reduction in the number of trainees supported. Stipend rates, however, would increase at the same pace as for FY 2012 at 2.0 percent, continuing a long-term strategy that NIH has used to try and keep stipend levels closer to salaries that could be earned in related occupations, to ensure that outstanding individuals continue to pursue biomedical research careers.

Funding for Intramural Research and Research Management and Support reflects would increase by 0.6 percent and 0.1 percent, respectively, compared to the FY 2012 Enacted level. Buildings and Facilities (B&F) funding will remain at the same level as FY 2012.

A more detailed description of the impact of the President's Budget request level by funding mechanism is provided in the Overall Appropriations (Tab 2) of this submission.

Other NIH-Supported Priorities

HIV/AIDS

As with the overall NIH budget request, NIH support for its HIV/AIDS research will be flat in FY 2013. This research is discussed in greater detail in the Office of AIDS Research section later in this volume. Consistent with the FY 2012 Enacted appropriations, support for the Global HIV/AIDS transfer to the Department of State is not included within this request, and is instead included directly within the Budget request for NIAID.

HHS Priority Goal

In support of the Secretary's priority goal to reduce cigarette smoking, NIH has identified research to prevent and control tobacco use and tobacco-related cancers as a public health priority. The Tobacco Control Research Branch of the National Cancer Institute leads and collaborates on research and disseminates evidence-based findings to prevent, treat, and control tobacco use. Activities include funding research grants and contracts, sponsoring conferences and symposia, and disseminating tobacco control science. In addition, NIH scientists conduct research and participate in diverse scientific and programmatic activities in support of national and international tobacco control efforts.

Overview of Performance

NIH's mission is to support science in the pursuit of fundamental knowledge about the nature and behavior of living systems, and the application of that knowledge to extend healthy lives and to reduce the burdens of illness and disability. Investments in basic biomedical and behavioral research make it possible to understand the causes of disease onset and progression, design preventive interventions, develop better diagnostics, and discover new treatments and cures. Realizing the benefits of fundamental biomedical discoveries depends on the translation of that knowledge into the development of new diagnostics, therapeutics, and preventive measures to improve health. Investments in translational research are leading to the identification of new targets and pathways for the development of new therapeutics.

The FY 2013 NIH Budget Request reflects the agency's long-standing commitment to invest strategically using performance-based analysis, as required under the GPRA Modernization Act of 2010. Through the continuous evaluation and strategic management of its research portfolio, the NIH focuses on funding research that shows the greatest promise for improving the overall health of the American people. In addition, the NIH continually seeks to identify and address high priority, unmet scientific opportunities and emerging public health needs. By managing its research portfolio to support key research priorities, the NIH ensures the most effective use of funds to achieve the greatest impact on the economic welfare and health of the nation. In particular, the NIH's strong peer review process, site visits, performance monitoring, multilevel advisory committees and councils, program evaluation and performance-based contracting enable the agency to ensure its investments generate results for the American people.

The NIH strives to achieve transparency and accountability by regularly reporting results, achievements, and the impact of its activities. The agency supports a wide spectrum of biomedical and behavioral research and engages in a full range of activities that enable research, its management, and the communication of research results. Because of this diversity and complexity, the NIH uses a set of performance measures that are representative of its activities and are useful for tracking progress in achieving performance priorities. This representative approach has helped the NIH to share progress of its performance priorities with HHS, the rest of the Executive Branch, the Congress, and the public.

The NIH performance measures reflect the agency's overall goals to advance basic biomedical and behavioral science, support translational research, and enhance the development of human capital and strengthen the scientific workforce. The measures also support the goals and objectives of the HHS Strategic Plan 2010-2015. In particular, the NIH substantially contributes to the HHS Strategic Goal 2 – Advance Scientific Knowledge and Innovation (Objective A: Accelerate the process of scientific discovery to improve patient care). For example, in FY 2013, the NIH will support research with the goals of: (1) making freely available to researchers the results of 300 high-throughput biological assays, screened against a library of 300,000 unique compounds that are expected to provide a scientific resource that will accelerate the discovery of protein functions that control critical processes such as development, aging, and disease; and (2) identifying and characterizing two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.

Moreover, in support of the President's goal of transforming and modernizing the U.S. health care system and the HHS Strategic Goal 1 – Strengthen Health Care (Objective C: Emphasize primary and preventive care linked with community prevention services), the NIH will continue to support research to identify three key factors influencing the scaling up of research-tested interventions across large networks of services systems such as primary care, specialty care and community practice.

Performance Management

Performance management at the NIH is an integrated and collaborative process to ensure that the agency is achieving its mission to conduct and support research to improve public health. At the agency level, the NIH Director sets priorities, monitors performance, and reviews results across the 27 Institutes and Centers (ICs) and the Office of the Director (OD). The OD is the central office that is responsible for setting policy for the NIH and for planning, managing, and coordinating the programs and activities of all NIH components. The NIH Director provides leadership to the ICs and helps identify needs and opportunities, especially for efforts that involve multiple ICs. Each IC and OD office carries out priority setting, performance monitoring, progress reviews, and makes adjustments based on progress achieved in their respective areas of science. In addition to the performance management processes that occur for the NIH research program, there are equivalent processes for administrative management functions.

The NIH performance framework includes: (1) priority setting with input from key stakeholders; (2) implementation and management of activities that support priorities; (3) monitoring and assessment of progress, and identification of successes and challenges; (4) oversight by IC leadership and OD office directors in assessing overall progress towards priorities and identification of best practices, appropriate next steps, and corrective actions (as needed); (5) incorporation of regular feedback from IC and OD office leadership to enhance activities; (6) regular reviews of priorities, progress, and outcomes by the NIH Director and IC Directors; and (7) regular review of performance and priorities by external expert review groups including grant peer review groups, Advisory Councils, and ad hoc working groups.

Qualitative and quantitative information is used to monitor progress and help to identify successes as well as failures in achieving short- and long-term goals. Supporting high performing research is a process of adapting to new developments or newly identified barriers, or shifting resources to pursue promising unanticipated results that may provide critical new information. Moreover, the impact of research may not be immediately known and may depend on additional development or on advances in other fields. Despite these challenges, NIH leadership is able to manage performance effectively by using the best available information to assess progress toward achieving priorities and making appropriate adjustments.

Research is an inherently collaborative endeavor and partnerships are crucial to achieving scientific research outcomes. The role of the extramural research community (the scientists at universities and hospitals across the country and around the world) as NIH's partner in research is well known. However, of increasing importance are partnerships with private companies, not-for-profit institutions, non-governmental organizations, other Federal agencies, and state and foreign governments. Joint research and training activities and other exchanges with such groups leverage NIH resources. Moreover, such partnerships facilitate valuable information feedback

loops that identify emerging needs, suggest important new research questions, and otherwise inform priority setting. Partnerships also provide access to populations that are essential to advancing knowledge. All scientific research carried out through NIH support is subjected to a rigorous and consistently applied review processes. For example, the Extramural Research Program, which oversees the largest category of NIH-funded research, utilizes two levels of peer review. The first level consists of chartered scientific review groups composed of outside experts in particular scientific disciplines. The second level is the National Advisory Councils of the various Institutes. For the Intramural Research Program, the progress of individual scientists and their laboratories is evaluated once every 4 years by Boards of Scientific Counselors composed of external experts. These reviews enable ongoing assessments of all intramural labs and the accomplishments of the scientists who contribute to them. It is through this well-honed system of peer review that the NIH can maintain its focus on supporting research of the highest possible quality.

The NIH approach to performance management is undergirded by the NIH Governance Structure. That structure includes the NIH Steering Committee⁸ and five standing Working Groups.⁹ Ad hoc working groups are established, as needed, to address emerging issues. The premise of the structure is that shared governance, which depends on the active participation of the IC Directors with the NIH Director, will foster the collaborative identification of corporate issues and a transparent decision-making process. With active participation by the IC Directors in NIH-wide governance, the NIH can maximize its perspective and expertise in the development and oversight of policies common to the NIH and its ICs. Through the governance process, corporate decisions are made; these may be long-term and strategic (e.g., facilities planning, budget strategy, research policy direction) or short-term and tactical (e.g., stipend levels, resource allocations and compliance oversight). This process does not include issues related to the setting of scientific priorities which is reserved for meetings of all IC Directors.

The NIH Director meets with the IC Directors on a bi-weekly basis, and scientific initiatives are discussed as well as major management issues that affect the agency. In addition, scientists—from within and outside the agency—are invited to present on new or emerging research opportunities. The NIH Director stays informed of priorities through regular, individual meetings with IC and OD Office Directors. Similarly, the IC Directors monitor performance through regular meetings with the Division Directors and Scientific/Clinical Directors in their respective ICs. Based on these reviews, leadership and their staff take appropriate actions to support research activities. For example, the reviews may lead to the development of new award programs for early career researchers, the development of new funding announcements for promising research areas, or new collaborations across the NIH and/or with other Federal and non-Federal partners. The NIH Director and senior leadership receive regular updates on the progress of the priorities, provide feedback, and incorporate the latest information into the NIH's overall planning and management efforts. This constant feedback loop enables the NIH to make critical adjustments periodically to align activities and target resources in support of its research priorities.

⁸ The NIH Steering Committee is composed of the NIH Director, Deputy Director (ex-officio), the Directors of NCI, NHLBI, and NIAID, as well as a balance of Directors from the smaller and medium sized institutes.

⁹ The five standing working groups are: Extramural Activities, Intramural, Information Technology, Facilities, and Management and Budget.

**National Institutes of Health
FY 2013 Congressional Justification**

Budget by HHS Strategic Goal

(Dollars in Millions)

HHS Strategic Goals	FY 2011 Actual	FY 2012 Enacted	FY 2013 President's Budget Request
1. Strengthen Health Care	\$129	\$151	\$278
1.A Make coverage more secure for those who have insurance	\$0	\$0	\$0
1.B Improve health care quality and patient safety and extend affordable coverage to the uninsured	\$0	\$0	\$0
1.C Emphasize primary & preventative care link with community prevention	\$129	\$151	\$278
1.D Reduce growth of health care costs while promoting high-value effective care	\$0	\$0	\$0
1.E Ensure access to quality culturally competent care for vulnerable populations	\$0	\$0	\$0
1.F Promote the adoption and meaningful use of health information technology	\$0	\$0	\$0
2. Advance Scientific Knowledge & Innovation	\$24,960	\$23,559	\$21,853
2.A Accelerate the process of scientific discovery to improve patient care	\$24,960	\$23,559	\$21,853
2.B Foster innovation at HHS to create shared solutions	\$0	\$0	\$0
2.C Invest in the regulatory sciences to improve food & medical product safety	\$0	\$0	\$0
2.D Increase our understanding of what works in public health and human services	\$0	\$0	\$0
3. Advance the Health, Safety, and Well-Being of American People	\$0	\$0	\$0
3.A Promote the csafety, well-being, resilience and healthy development of children and youth safety	\$0	\$0	\$0
3.B Promote economic & social well-being for individuals, families and communities	\$0	\$0	\$0
3.C Improve the accessibility and quality of supportive services for people with disabilities and older adults	\$0	\$0	\$0
3.D Promote prevention and wellness	\$0	\$0	\$0
3.E Reduce the occurrence of infectious diseases	\$0	\$0	\$0
3.F Protect Americans' health and safety during emergencies, and foster resilience in response to emergencies	\$0	\$0	\$0
4. Increase Efficiency, Transparency, and Accountability of HHS Programs	\$637	\$938	\$1,368
4.A Ensure program integrity and responsible stewardship of resources	\$637	\$938	\$1,368
4.B Fight fraud and work to eliminate improper payments	\$0	\$0	\$0
4.C Use HHS data to improve American health and well-being of the American people	\$0	\$0	\$0
4.D Improve HHS environmental, energy, and economic performance to promote sustainability	\$0	\$0	\$0
5. Strengthen the Nation's Health & Human Service Infrastructure & Workforce	\$5,200	\$6,212	\$7,361
5.A Invest in HHS workforce to meet America's health and human service needs today & tomorrow	\$5,200	\$6,212	\$7,361
5.B Ensure that the Nation's health care workforce meets increased demands.	\$0	\$0	\$0
5.C Enhance the ability of the public health workforce to improve health at home and abroad	\$0	\$0	\$0
5.D Strengthen the Nation's human service workforce	\$0	\$0	\$0
5.E Improve national, State & local surveillance and epidemiology capacity	\$0	\$0	\$0
TOTAL	\$30,926	\$30,860	\$30,860

NATIONAL INSTITUTES OF HEALTH
FY 2013 Congressional Justification
Budget Mechanism - Total ¹
(Dollars in Thousands)

MECHANISM	FY 2011		FY 2012		FY 2013		Change	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Grants:								
<u>Research Projects:</u>								
Noncompeting	26,166	\$11,865,527	25,614	\$11,937,753	24,837	\$11,548,696	(777)	(\$389,057)
Administrative Supplements	1,253	195,043	1,187	171,987	1,120	159,051	(67)	(12,936)
<u>Competing:</u>								
Renewal	2,108	1,039,341	2,203	1,015,652	2,329	1,199,173	126	183,521
New	6,572	2,671,269	6,512	2,673,075	7,057	2,847,190	545	174,115
Supplements	26	10,858	28	10,445	29	10,103	1	(342)
Competing	8,706	\$3,721,468	8,743	\$3,699,172	9,415	\$4,056,466	672	\$357,294
Subtotal, RPGs	34,872	\$15,782,038	34,357	\$15,808,912	34,252	\$15,764,213	(105)	(\$44,699)
SBIR/STTR	1,494	\$646,222	1,587	\$680,351	1,636	\$699,262	49	18,911
Research Project Grants	36,366	\$16,428,260	35,944	\$16,489,263	35,888	\$16,463,475	(56)	(\$25,788)
<u>Research Centers:</u>								
Specialized/Comprehensive	1,227	\$2,237,467	1,234	\$2,281,719	1,196	\$2,224,520	(38)	(\$57,199)
Clinical Research	72	437,873	59	406,028	62	406,586	3	558
Biotechnology	95	147,396	103	147,571	88	140,567	(15)	(7,004)
Comparative Medicine	50	137,719	47	136,210	47	135,945	0	(265)
Research Centers in Minority Institutions	23	59,136	23	59,136	23	58,697	0	(439)
Research Centers	1,467	\$3,019,591	1,466	\$3,030,664	1,416	\$2,966,315	(50)	(\$64,349)
<u>Other Research:</u>								
Research Careers	3,919	\$625,950	3,909	\$635,122	3,908	\$634,646	(1)	(\$476)
Cancer Education	90	32,590	90	32,590	90	32,606	0	16
Cooperative Clinical Research	414	448,384	418	454,591	406	446,679	(12)	(7,912)
Biomedical Research Support	135	70,232	130	68,026	130	68,163	0	137
Minority Biomedical Research Support	367	104,455	374	111,280	367	109,182	(7)	(2,098)
Other	1,750	521,623	1,833	531,466	1,817	531,992	(16)	526
Other Research	6,675	\$1,803,234	6,754	\$1,833,075	6,718	\$1,823,268	(36)	(\$9,807)
Total Research Grants	44,508	\$21,251,085	44,164	\$21,353,002	44,022	\$21,253,058	(142)	(\$99,944)
<u>Ruth L. Kirschstein Training Awards:</u>								
Individual Awards	3,027	\$127,442	3,020	\$128,791	2,961	\$128,672	(59)	(\$119)
Institutional Awards	13,861	644,324	13,650	648,970	13,400	646,646	(250)	(\$2,324)
Total Research Training	16,888	\$771,766	16,670	\$777,761	16,361	\$775,318	(309)	(\$2,443)
Research & Development Contracts (SBIR/STTR)	2,386 113	\$3,227,139 \$38,067	2,369 108	\$2,967,896 \$44,372	2,391 107	\$3,075,882 \$46,357	22 (1)	\$107,986 \$1,985
Intramural Research		\$3,398,791		\$3,399,495		\$3,420,425	0	20,930
Research Management and Support		1,526,330		1,533,406		1,535,097	0	1,691
Office of the Director - Appropriation ²		\$1,454,323		\$1,457,381		\$1,429,161		(\$28,220)
Office of the Director - Other		605,428		608,471		580,251		(28,220)
ORIP & SEPA ²		305,874		303,980		303,980		0
Common Fund ²		543,021		544,930		544,930		0
Buildings and Facilities ³		57,749		133,228		133,228		0
Appropriation		49,900		125,308		125,308		0
Type 1 Diabetes ⁴		(150,000)		(150,000)		(150,000)		(0)
Subtotal, Labor/HHS Budget Authority		\$30,688,288		\$30,623,259		\$30,623,259		(\$0)
Interior Appropriation for Superfund Res.		79,054		78,928		78,928		0
Total, NIH Discretionary B.A.		\$30,767,342		\$30,702,187		\$30,702,187		(\$0)
Type 1 Diabetes		150,000		150,000		150,000		0
Total, NIH Budget Authority		\$30,917,342		\$30,852,187		\$30,852,187		(\$0)
NLM Program Evaluation		8,200		8,200		8,200		0
Total, Program Level		\$30,925,542		\$30,860,387		\$30,860,387		(\$0)

¹ All items in italics are "non-adds"; items in parenthesis are subtractions.

² Number of grants and dollars for the Common Fund, ORIP and SEPA components of OD are distributed by mechanism and are noted here as a non-add. The Office of the Director - Appropriations also is noted as a non-add since these funds are accounted for under OD - Other.

³ Includes B&F appropriation plus construction dollars appropriated to NCL.

⁴ Number of grants and dollars for mandatory Type I Diabetes are distributed by mechanism above; therefore, Type I Diabetes amount is deducted to provide subtotals only for the Labor/HHS Budget Authority.

⁵ Reflects NCATS reorganization in FY 2012 and the \$998K transfer from DHHS for the Interagency Autism Coordinating Committee.

⁶ Reflects Omnibus Across-the-Board rescission of 0.189% for Labor/HHS discretionary BA and 0.16% rescission for Superfund as well as Secretary's Transfer of \$8.7M.