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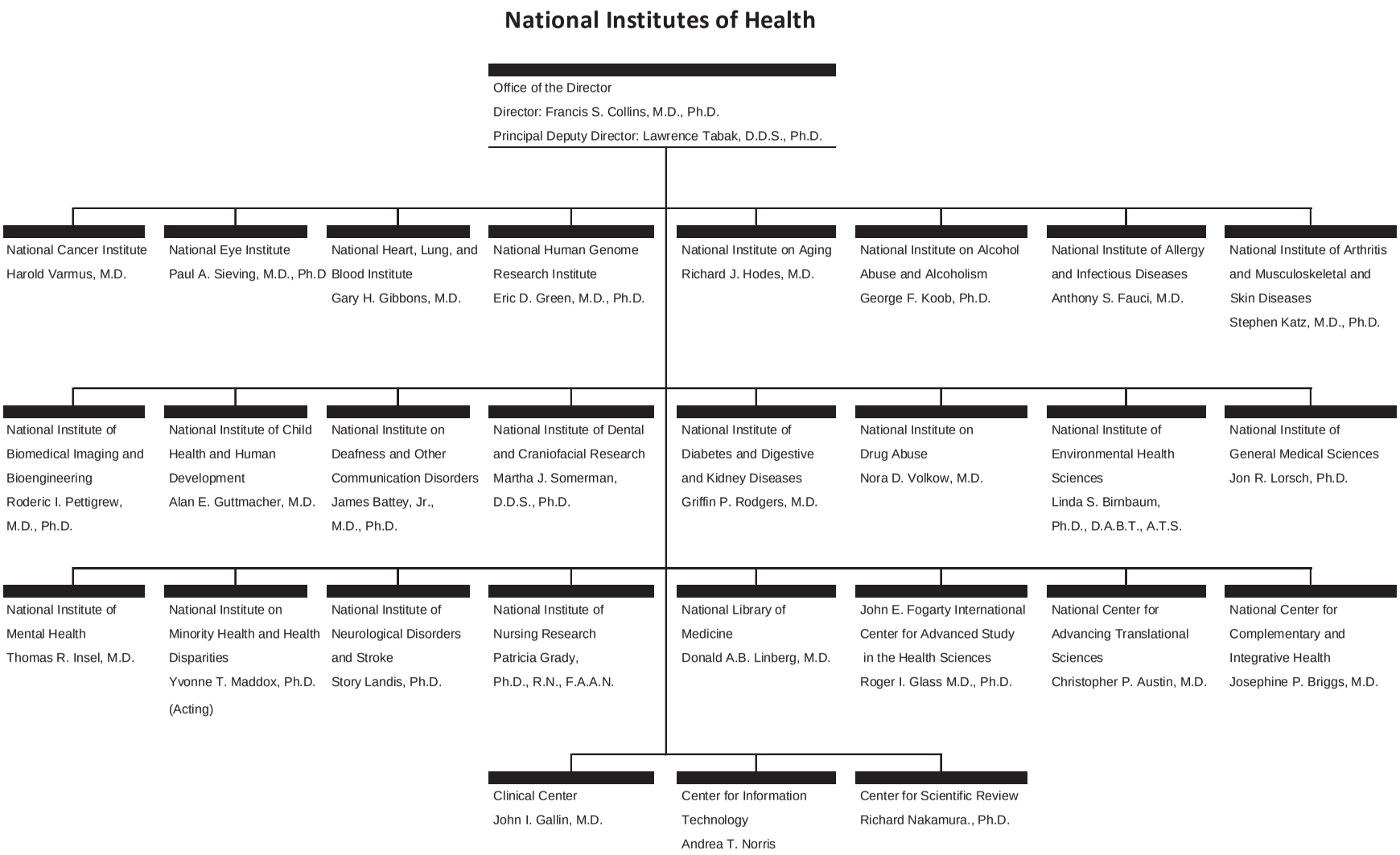

## INTRODUCTION AND MISSION

The mission of the National Institutes of Health (NIH) is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. In pursuit of this mission, NIH conducts or supports research designed to understand the basic biology of human health and disease; apply this understanding toward designing new approaches for preventing, diagnosing, and treating disease and disability; and ensure that these new approaches are available to all.

As the Nation's medical research agency and the largest source of funding for biomedical and behavioral research in the world, NIH plays a unique role in turning basic scientific discovery into tangibles that improve health. A significant and enduring investment by NIH in basic research today guarantees the breakthroughs in health care tomorrow. To realize such breakthroughs, NIH also invests in research that will translate these basic findings into the delivery of effective health care. Novel research methods stimulated by technological advances, including the generation of complex data sets, are facilitating extraordinary opportunities to address previously unanswerable questions about biology, behavior, and medicine. This robust research enterprise depends upon NIH's continued innovation, as it seeks to recruit and retain the Nation's brightest minds into successful scientific careers. With continued support, NIH contributes significantly to the economic engine that drives American competitiveness in science and technology and will realize a Nation in which all Americans enjoy long, healthy lives.

# ALL PURPOSE TABLE

| (Dollars in Thousands) | FY 2014 Actual | FY 2015 Enacted[1] | FY 2016 President's Budget | FY 2016 Request +/- FY 2015 Enacted |
|---|---|---|---|---|
| **Total, NIH Program Level** | **$30,070,062** | **$30,311,349** | **$31,311,349** | **$1,000,000** |
| **Less funds allocated from different sources:** | | | | |
| Mandatory Type 1 Diabetes Research | -139,200 | -150,000 | -150,000 | 0 |
| PHS Program Evaluation | -8,200 | -715,000 | -847,489 | -132,489 |
| **Total, NIH Discretionary Budget Authority** | **$29,922,662** | **$29,446,349** | **$30,313,860** | **$867,511** |
| Interior Budget Authority | -77,349 | -77,349 | -77,349 | 0 |
| **Total, NIH Labor/HHS Budget Authority** | **$29,845,313** | **$29,369,000** | **$30,236,511** | **$867,511** |
| *Number of Competing RPGs* | *9,168* | *9,076* | *10,303* | *1,227* |
| *Total Number of RPGs* | *34,332* | *34,206* | *35,447* | *1,241* |
| *FTEs* | *18,048* | *18,150* | *18,150* | *0* |

[1] Excludes Ebola-related funding.

## OVERVIEW OF BUDGET REQUEST

For Fiscal Year (FY) 2016, NIH requests a total program level of $31.3 billion which is $1.0 billion above the FY 2015 Enacted level. This request reflects both the President's and the Secretary's commitment to improving the health of all Americans and to maintaining the country's leadership in the biomedical sciences. For more than a hundred years, NIH has advanced the understanding of human health and disease through its investments in biomedical research, and the results of this research have helped improve health, lengthen life, and reduce illness and disability for many generations. NIH's work produces important secondary benefits to the Nation as well, including job creation, regional and global economic activity, international competitiveness, intellectual property, and commercializable products, to name a few. For example, a recent health and financial analysis of one clinical trial undertaken through NIH's Women's Health Initiative has demonstrated the robust return that NIH provides to the American public. The study estimated that one postmenopausal hormone therapy trial resulted in long-term financial and health outcomes worth $37.1 billion in net economic gain, a return of approximately $140 on every dollar invested in the trial.[1]

In order to maintain excellence, NIH must continue to fund a strong, diverse portfolio of biomedical research, flexible enough to capitalize on scientific opportunities and to respond to urgent public health needs as they arise. For example, the recent Ebola epidemic in West Africa allowed NIH to demonstrate this flexibility in responding to a public health emergency. Numerous NIH-funded scientists utilized established biomedical research infrastructure to identify the source and track the spread of the epidemic using advanced genetic sequencing technologies, develop multiple promising vaccine candidates in tandem with the private sector, perform Phase I vaccine safety and efficacy clinical trials, and take steps to perform advanced clinical vaccine testing in an afflicted country.

To strike this delicate balance in its biomedical research portfolio, in FY 2016, NIH will focus on the following priority themes:

1. Unraveling Life's Mysteries through Basic Research
2. Translating Discovery into Health
3. Harnessing Data and Technology to Improve Health
4. Preparing a Diverse and Talented Biomedical Research Workforce

By pursuing these priorities, NIH will continue to take on the critical scientific challenges that must be faced to improve health, reduce disability, and drive the engines of discovery and innovation. Often these challenges are ones that NIH is uniquely poised to pursue because of the Agency's expertise, resources, and deep commitment to health and the public good.

### Theme 1: Unraveling Life's Mysteries through Basic Research

As the largest funder of basic biomedical science in the world, NIH has a long tradition of supporting transformative basic science breakthroughs. Basic, foundational research is a major driver of progress across the biological and behavioral sciences – advances in fields such as genomics, proteomics, stem cells, the microbiome, imaging, and other technologies have

[1] See: http://www.ncbi.nlm.nih.gov/pubmed/24798522

transformed our understanding of how life works, have led to the discovery of more than a thousand risk factors for disease, and have yielded inestimable benefits to public health. Basic research often paves the way for unexpected scientific advances and unanticipated health applications. For example, NIH-funded scientists built upon the finding that a single light-sensitive protein controls the movement of green algae toward sunlight to develop optogenetics, a game-changing technique that allows scientists to selectively turn neurons in the brain on or off merely by exposing them to light. Similarly, early advances in the field of nanoscience laid the groundwork for developing innovative, body-friendly nanotools to help scientists build synthetic biological devices, such as miniature, implantable pumps for drug delivery, or tiny sensors to scan for the presence of infectious agents that could spell trouble for the body. By supporting a broad basic research portfolio, NIH helps to forge the biomedical breakthroughs of tomorrow. Below are a few examples of basic science areas of particular promise for FY 2016.

*Single Cell Biology*

Individual cells within the same tissues, organs, or parts of the body may differ dramatically, and these differences can have important consequences for the overall health of an organism. Yet, because of technical limitations, most *in vivo* biological research until very recently has been focused on tissue segments involving millions of cells. New technologies and experimental approaches now hold out the promise of analyzing and targeting single cells within large, complex biological environments.

Through a focus on single cell biology, NIH is challenging scientists to address significant hurdles that currently exist in measuring the given "state" of a cell, defining normal cell-to-cell variation, detecting the impact of different environmental changes, and understanding how collections of diverse cell types function together as part of a larger whole. Through the Common Fund's Single Cell Analysis Program, NIH funded nearly $8 million in research in 2014 to unravel the workings of single cells.

Not only can scientists now study individual cells in their native state, NIH-funded scientists recently developed a powerful new tool called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), which allows precise targeting of genes for deletion, addition, activation, or suppression – with such specificity that it amounts to performing genetic microsurgery, potentially at the level of a single cell. The method harnesses a protein that is involved in a bacteria's adaptive immune response that works through precise targeting of DNA. CRISPR has been used to alter genes in cells from bacteria, mice, and humans, and even to engineer monkeys with specific mutations that could serve as more accurate models of human disease. By cultivating the next generation of technologies for single cell analysis, NIH-funded scientists are primed to uncover fundamental biological principles and ultimately improve the detection and treatment of disease.

*Advanced Cellular Imaging*

Advanced imaging techniques allow scientists to peer into the human body with pinpoint accuracy and reveal the inner workings of living tissue in extraordinary detail. Several recent advances in imaging technology by NIH-funded researchers are making it easier to produce high-resolution, three-dimensional molecular movies and even capture nanoscale chemical reactions occurring in real time. Three cellular imaging techniques – X-ray free-electron lasers, electron cryomicroscopy (cryo-EM), and light microscopy – illustrate how quickly these imaging technologies are evolving. For one, newly developed X-ray free-electron lasers are a major

innovation that produces X-ray pulses faster and more powerfully than ever before. With the capability of accelerating particles to nearly the speed of light, free-electron X-ray lasers are strong enough to pierce through steel and fast enough to capture strobe-like images of molecular motions. Second, innovations in cryo-EM are using faster, more efficient cameras to obtain pictures of biological complexes at near-atomic resolution. Lastly, continual refinements in light microscopy have made it possible, for example, to conduct cellular-level brain imaging in freely moving animals and to stage high-throughput, automated screening of drug effects in animal models of disease.

With all of this progress, a number of technical hurdles remain, such as boosting the power and brightness of free-electron lasers, further increasing image resolution, and developing novel approaches to analyzing the deluge of data that advanced cellular imaging tools produce. In FY 2016, NIH will continue to fund scientists who are pushing the boundaries of biological imaging capabilities.

*The 4D Nucleome*

While great strides have been made in mapping the human genome and understanding the many factors that control gene expression in health and disease, our increasing knowledge continues to lead to big questions and new scientific opportunities. From research on the human genome came a refined appreciation for the epigenome, the host of non-DNA elements that control gene expression and can be strongly influenced by the environment. Likewise, there is a growing appreciation for the critical role of the spatial, three-dimensional organization of the nucleus, the physical structure within each cell that houses most DNA. Recent basic research suggests that the spatial distribution of DNA and other DNA-interacting molecules within the nucleus is far from random and changes dynamically over time, adding yet a fourth dimension to an already complex picture – thus, an emerging line of research focuses on unraveling the 4D nucleome. Harmful alterations in the organization of the nucleome are associated with rare genetic disorders as well as certain cancers and premature aging syndromes.

Beginning in FY 2015 and ramping up in FY 2016, the 4D Nucleome Initiative will support basic research into the architecture of the nucleus, how it changes over time, as well as its relationship to gene expression, cellular health, and disease states. NIH-funded scientists also will explore the role of epigenetic modifications in the four dimensions of DNA organization inside the nucleus, as well as develop tools and databases to encourage collaboration and accelerate the study of the 4D Nucleome. In the long term, the primary goal of this program is to understand how the physical structure of genetic material within the nucleus influences the function of the genome in order to better understand complex disease pathways, which could yield important clues to developing a new generation of diagnostics and therapeutics.

*The BRAIN Initiative*

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative was launched by the President on April 2, 2013, as a bold new effort to revolutionize our understanding of the human brain. The complexity of the human brain was once thought to be beyond our understanding – the brain comprises nearly 100 billion nerve cells that make an astounding 100 trillion connections. Through this initiative, NIH and its partners are driving the development and use of innovative technologies to produce a clearer, dynamic picture of the brain that can show, for the first time, how individual cells and complex neural circuits interact in both time and space.

This multi-agency initiative leverages the unique strengths of NIH, the Defense Advanced Research Projects Agency (DARPA), the National Science Foundation (NSF), the Food and Drug Administration (FDA), and the Intelligence Advanced Research Projects Activity (IARPA), as well as private funders. Given the ambitious goals of the BRAIN Initiative, success will require ideas from the best scientists and engineers across many diverse disciplines. NIH's funding priorities have been guided by a high-level working group of the Advisory Committee to the NIH - the NIH BRAIN working group - which was composed of expert scientists around the country. Its planning process sought input broadly from the scientific community, patient advocates, and the general public.

The NIH BRAIN working group first released an interim report in December 2013, which informed and guided funding priorities for FY 2014 BRAIN initiative funding. On June 5, 2014, the working group released its much-anticipated recommendations for a strategy encompassing FY 2016 – FY 2025. The plan includes a bold agenda for progress, including specific goals, milestones, and deliverables. Nine specific objectives are geared toward developing novel, cutting-edge tools to image and control neural activity in order to better understand the architecture and function of the brain. Ultimately, the technologies developed under the BRAIN Initiative may help reveal the underlying pathology in a vast array of brain disorders and provide new therapeutic avenues to treat, cure, and even prevent neurological and psychiatric conditions, such as Alzheimer's disease, autism, depression, schizophrenia, and addiction.

On September 30, 2014, NIH awarded the initial round of grants for the BRAIN Initiative, totaling $46 million. These grants included six funding initiatives, covering a wide array of topics from better understanding the cells and circuits of the brain to developing better tools to measure and manipulate their activity to the next generation of non-invasive human functional imaging. These funds represent only the initial investment in these tools and approaches for understanding the brain. To accomplish the initiative's ambitious goals, and to allow the United States to lead the world in this cutting-edge area of science, the working group recommended a significant ramp-up in funding. The request includes $135 million an increase of $70 million for BRAIN in FY 2016.

**Theme 2: Translating Discovery into Health**

NIH is heavily invested in translating its basic scientific discoveries into fruitful health applications. Translational sciences turn observations in the laboratory and clinic into effective interventions that improve the health of individuals and the public, from diagnostics and therapeutics to medical procedures, behavioral changes, and disease prevention strategies. All of NIH's 27 Institutes and Centers are involved in this effort; below are a few examples of areas of special opportunity in FY 2016.

*Precision Medicine*

Historically, medical practitioners have had to make recommendations about disease prevention and treatment based largely on the expected response of an average patient. However, recent advances in technology, along with decreasing costs of DNA sequencing, have developed a compelling and innovative approach to medicine by using individual variability. This emerging practice is known as precision medicine.

Precision medicine allows treatments to be tailored to the individual characteristics of each patient. To accomplish this, scientists and physicians must understand human variability and

identify individuals who differ in the susceptibility to a particular disease, in the trajectory of a disease, or in response to a specific treatment. In this way, specific preventive or therapeutic interventions can be adapted for each patient–avoiding needless treatment and expense for those who will not benefit.

NIH understands the importance of treating disease at an individual level, and has made precision medicine a priority. In FY 2014, two cancer precision medicine clinical trials commenced, both capitalizing on the infrastructure of the National Clinical Trials Network supported by the National Cancer Institute (NCI). The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials, or ALCHEMIST, will identify early-stage lung cancer patients with tumors that have certain uncommon genetic changes. Patients will receive one of two supplemental treatments specifically targeted to these genetic alterations to determine if the drugs prevent cancer recurrence and prolong life. The Lung Cancer Master Protocol (Lung-MAP) trial for patients with advanced squamous cell lung cancer will test four experimental drugs. This trial is a unique public-private collaboration between NIH, non-profit organizations, and pharmaceutical companies. Patients are assigned to a particular drug (or "arm" of the trial) based on the results of a genetic screen for cancer-related genes. Unlike previous clinical trials, Lung-MAP tests patients for many biomarkers simultaneously to assess compatibility with several different treatment options. This innovative trial design could be pivotal as advances in precision medicine make this type of treatment possible.

As part of the President's multi-agency Precision Medicine Initiative, NIH plans to spend $200 million on precision medicine in FY 2016. The battle against cancer has been leading the way in precision medicine for many years. To capitalize on these successes, the FY 2016 request proposes $70 million to expand current cancer genomics research to initiate new studies of how a tumor's DNA can be used to predict and treat tumor cells that develop resistance to a therapy, apply new non-invasive methods to track response to therapy, and explore the efficacy of new combinations of cancer drugs targeted to specific tumor mutations. In addition, to harness the full potential of precision medicine across many diseases, NIH proposes $130 million to launch a national research cohort of a million or more individuals, primarily those who have already participated in clinical research studies, who volunteer to share their genetic information in the context of other health data over time. This information will be linked to their electronic health records, while ensuring privacy protections are in place. A database of this scale will lay the foundation for a wealth of new research studies which promises to lead to new prevention strategies, and novel therapeutics and medical devices. It will also help improve how drugs are prescribed, allowing a more optimum choice of the right drug at the right dose for the right person.

*Ebola Virus Research and Vaccine Development*

Ebola virus disease can cause severe illness and death in humans and other primates. In early 2014, the first cases of a new Ebola virus outbreak were reported in West Africa - now the largest and most complex Ebola outbreak in history.

Alongside colleagues throughout the Federal Government, NIH sought to understand how this virus emerged as well as how to reduce or eliminate the threat it presents to public health at home and abroad. NIH-funded researchers used advanced genomic sequencing technologies to identify the single point of transmission from an animal host to a human in the current outbreak.

The findings highlight how NIH basic science investments can be deployed rapidly to assist in tracing origins of newly emerging microbial threats.

As there are yet no approved drugs or vaccines to fight Ebola virus disease, prompt diagnosis and aggressive supportive care can improve patient survival. Due in part to its support for Ebola vaccine development since 2001, NIH started several Phase I clinical trials of investigational, human Ebola vaccines in the fall of 2014. These trials used vaccines created from public private partnerships with pharmaceutical companies. Initial results are promising, and NIH will learn from the results and improve these vaccines with the goal of initiating more advanced, Phase II/III clinical trials of investigational Ebola vaccines in affected countries.

NIH will continue to provide input and direction for key policy decisions related to the Ebola response. For example, clinical researchers are developing a master protocol for comparing robust supportive care with experimental therapies in patients infected with Ebola at designated treatment facilities in the United States. Furthermore, the additional $238 million provided in emergency appropriations in FY 2015 will help NIH to perform the in-country advanced clinical trials necessary to combat the disease along with accelerating the identification and evaluation of new pre-clinical prevention and treatment approaches for Ebola.

*Stem Cells*

Recent research has demonstrated that stem cells have the remarkable potential to develop into many different cell types in the body. In many bodily tissues, stem cells serve as a kind of internal repair system, dividing extensively to replenish other cells as long as the person or animal is alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. A recently developed research technique, which garnered the 2012 Nobel Prize in Physiology or Medicine, now makes it possible to create a new type of stem cell called an induced pluripotent stem (iPS) cell in the laboratory – iPS cells are derived from mature cells, typically from a patient's skin or blood, which researchers can reprogram back to an immature state. These cells can then be turned into a wide variety of cell types, including liver cells, neurons, cardiac cells, and blood cells. NIH-funded scientists are studying iPS cells and other types of stem cells, not only to understand better cell function and disease pathways, but also to develop therapies for a variety of diseases and disabilities, including Parkinson's disease, amyotrophic lateral sclerosis (ALS), spinal cord injuries, heart disease, diabetes, and arthritis. For example, an NIH intramural scientist is pursuing preclinical efficacy and safety studies with retinal pigment epithelium tissue, developed from a patient's own skin cells using iPS technology, to treat age-related macular degeneration, a leading cause of blindness in the elderly. Another condition for which stem cell treatment has shown particular promise is sickle cell disease (SCD). SCD is a serious inheritable disorder in which the body makes sickle-, or crescent-shaped red blood cells, which, unlike their normal counterparts, are stiff and sticky and tend to block blood flow in limbs and organs. Blocked blood flow can cause pain and lead to organ damage, and also can raise the risk for serious infection. Currently, hematopoietic stem cells, or blood-producing stem cells found in bone marrow and peripheral blood, are used to treat SCD, but transplant rejection is a major risk, and the treatments can have severe consequences and life-threatening complications. The advent of iPS cell technology has raised the possibility of a novel therapeutic strategy – skin cells from a patient could be programmed to become pluripotent and self-renewing, and then engineered (perhaps using new genome editing techniques) to correct the sickle mutation. Differentiating those cells into hematopoietic stem

cells and infusing them back to the individual could provide a potential cure, with no risk of transplant rejection.

*Influenza Vaccines*

Influenza, or the flu, is a respiratory infection that can be caused by several different viral strains. Most people who become infected feel better within a week, although they may have a lingering cough and tire easily for a while longer. An estimated 5 to 20 percent of Americans are infected during each flu season, which typically lasts from October to March. For the elderly, newborns, pregnant women, immunocompromised persons, and people with certain chronic illnesses, the flu and its complications can be life-threatening, and each year more than 200,000 people are hospitalized. Although most recover from the illness, between 3,000 and 49,000 Americans die as a result of the flu and its complications every year.

Currently, receiving the seasonal vaccine is the best way to prevent the flu, despite the scientific 'guess work' used to select the strain most likely to emerge each year and the risk of new emerging strains with pandemic potential. Using cutting-edge knowledge of immunology, genomics, and structural biology, NIH-funded scientists are making significant progress in the development of a universal influenza vaccine. A universal vaccine could confer decades-long protection from any influenza strain, be it seasonal or a possible pandemic strain (e.g., H1N1, H5N1, and H7N9). Strain detection and vaccine development are complicated and time consuming activities, so NIH works closely with its Federal Government agency partners, including the Centers for Disease Control and Prevention (CDC) and FDA, as well as experts in academia, industry, and foreign governments. In FY 2016, the Biological Advanced Research and Development Authority (BARDA) and NIH will work with HHS to prioritize activities that best align with the ongoing HHS strategy to develop a universal influenza vaccine. An increase of $20 million is requested in FY 2016 to accelerate this research.

*HIV Vaccine and Cure Research*

An estimated 36 million people have died from AIDS since the first cases were reported in 1981, while more than 35 million people worldwide are now thought to be infected with HIV. NIH's long-term support of HIV/AIDS research has resulted in more than 30 FDA-approved therapeutics and various strategies to reduce the spread of the virus. Moreover, a top priority for NIH remains developing a safe, effective, and affordable HIV vaccine. Such a vaccine would need to be used in combination with other prevention, treatment, and behavioral approaches in order to end the AIDS pandemic.

NIH-funded researchers are designing and evaluating safe and effective vaccine candidates to prevent HIV infection. NIH is currently investigating the reasons for the modest efficacy (31 percent protection) of the HIV vaccine candidates used in the RV-144 clinical trial conducted in Thailand in 2009 and will seek to achieve significantly better results with future vaccine candidates. NIH has funded two new promising HIV vaccine initiatives and also is exploring in clinical trials whether or not passively transferred neutralizing antibodies can protect against HIV infection. Marking the 25$^{th}$ annual World AIDS Day, President Obama announced in December 2013 that the NIH will redirect $100 million of AIDS research funds to expand research towards a cure for HIV. Many promising recent basic and translational research advances targeting viral reservoirs, pockets of cells or tissues where HIV can hide and evade the host immune system, suggest that a complete cure, or at least lifelong remission, of HIV infection may be possible. The majority of the funds will support basic HIV research, along with advanced studies focused

on improving animal models, drug development, preclinical testing of antiretroviral compounds, and clinical evaluation of therapeutic vaccines and other immune enhancers. Research into prevention strategies, understanding how certain factors affect treatment and/or disease progression, and the increased incidence of co-morbidities in patients on lifelong treatment also will be addressed. The increased attention given to HIV cure research will add to previous successes to treat HIV and continue the NIH's effort to move towards an AIDS-free generation. An increase of $100 million is requested in FY 2016 to expand NIH's HIV/AIDS research.

*Antimicrobial Resistance (AMR)*

Public health surveillance has documented an alarming increase in AMR in pathogenic bacteria, especially those that cause hospital-acquired infections, tuberculosis, and gonorrhea. AMR is an inevitable outcome of the evolutionary principle that organisms will mutate to escape lethal selective pressure; by acquiring genetic mutations and reproducing rapidly, some bacteria can evade destruction by drugs. As long as antibiotics are used to kill bacteria, resistance will continue to emerge. This process is exacerbated by the overuse and misuse of existing antimicrobial drugs. More than 70 percent of bacteria that cause healthcare-associated infections in the United States are resistant to at least one commonly used antibiotic, and bacteria resistant to all known antibiotics are appearing with increasing frequency. According to CDC, antibiotic resistance in the United States costs an estimated $20 billion per year in excess health care costs, $35 million in other societal costs, and more than 8 million additional days that people spend in the hospital. Each year in the United States, more than 2 million people acquire serious infections with bacteria that are resistant to one or more of the antibiotics designed to treat those infections. At least 23,000 people die each year as a result of these infections, and many more die from other conditions that were complicated by an antibiotic-resistant infection.

Recognizing the growing public health threat of AMR, the Administration has issued its *National Strategy for Combating Antibiotic-Resistant Bacteria*. In accordance with this Strategy, NIH (in concert with CDC, FDA, and the U.S. Department of Agriculture), is engaging in a number of key efforts designed to reverse the trend of illness and death due to increasing bacterial resistance to antimicrobials and address a major emerging threat to public health. First, to help ensure that antibiotics are prescribed appropriately, NIH will spur the development of new, rapid diagnostics. In collaboration with BARDA, FDA, and CDC, a competition is being designed for the development of a rapid diagnostic test that will be of great clinical and public health utility in combating AMR. A prize or prizes totaling at least $20 million will be announced by the end of FY 2016 and later awarded to the winning group(s) with the goal of incentivizing the development of a transformative diagnostic. Second, NIH will develop a national database of genomic sequence data on all reported human infections with antibiotic-resistant microorganisms. This will provide a critically needed resource for surveillance, epidemiology, and basic research into the mechanisms underlying the emergence of antimicrobial resistance. Third, NIH will launch a large-scale effort to characterize and understand drug resistance, focusing on the changes in host/pathogen molecular interactions that occur as bacteria develop resistance in response to antibiotic treatment. This knowledge is essential to developing accurate diagnostics and new therapeutic approaches. Fourth, NIH will expand its Antibiotic Resistance Leadership Group to create a rapid response clinical trial network that is ready to test new antibiotics on individuals infected with highly resistant strains. The request includes $461 million an increase of $100 million in FY 2016 to support the National Strategy.

*Accelerating Medicines Partnership (AMP)*

While technological advances have produced a wealth of data on the biological causes of disease, translating these discoveries into treatments has been far more difficult. Choosing the wrong drug target often results in failures in the drug development process, costing time, money, and, ultimately, lives. Developing a new drug typically takes well over a decade and has a failure rate of more than 95 percent, with many failures occurring late in the process. As a result, each success costs more than $1 billion.

The good news is that researchers have identified more than a thousand new potential targets for drug therapy in the last five years, offering an encouraging path forward. AMP seeks to spur entirely new approaches to the development of the next generation of drugs in order to increase the number of new diagnostics and therapies for patients while also reducing the time and cost of their development. It is essential for the pharmaceutical enterprise to pinpoint the right biological targets much earlier in the drug development process. AMP represents an unprecedented partnership between NIH, the Foundation for the NIH, FDA, 10 pharmaceutical companies, and a number of non-profit organizations. By focusing on optimizing how disease targets are identified and validated for drug design, AMP aims to help drug researchers choose the right targets faster. The AMP partnership plans to invest close to $230 million over five years, with total costs shared equally between NIH and the industry partners. The first AMP projects are focused on Alzheimer's Disease, Type 2 Diabetes, and the autoimmune disorders of lupus and rheumatoid arthritis. As this model gains in scientific strength, it is expected that other companies may join, and other disorders can be proposed for inclusion. A critical component of this collaboration is that industry partners have agreed to make AMP data and analyses publicly accessible to the broader biomedical research community. In FY 2016, NIH expects to spend $23 million for this initiative, the same level as in FY 2015.

*Alzheimer's Disease (AD)*

AD is a progressive, and, at present, irreversible brain disease that slowly destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks of daily living. The disease progresses in three stages, from a preclinical stage where no symptoms are present, to a middle stage of mild cognitive impairment, and ending with a final stage of Alzheimer's dementia. The time from diagnosis to death varies by person; it can be as little as three or four years if the person is older than 80 when diagnosed, but it can be as long as 10 or more years if the person is younger. Estimates vary, but experts suggest that as many as five million Americans age 65 and older have AD. Although treatment can help manage symptoms in some people, currently there is no cure for this devastating disease.

NIH supports a comprehensive program of research on AD. NIH focuses on basic neuroscience research, epidemiologic studies to identify risk and protective factors for cognitive impairment and AD, genetic studies to identify risk and protective genes, clinical studies to identify biomarkers for early disease diagnosis and for disease progression, and testing of interventions to prevent and treat the disease. NIH works with many partners and its coordination efforts have been facilitated greatly by the recent launch of the International Alzheimer's Disease Research Portfolio (IADRP), a publicly available database to capture the full spectrum of current AD research investments and resources, both in the United States and internationally. Developed by the National Institute on Aging (NIA) in collaboration with the Alzheimer's Association, the

IADRP will enable public and private funders of AD research to coordinate research planning, leverage resources, avoid duplication of funding efforts, and identify new opportunities in promising areas. Along with NIA, more than 20 NIH Institutes and Centers and a number of other Federal and non-Federal agencies from around the world contribute to the database.

Turning the tide on AD is a domestic and international priority. NIH's long-term planning efforts are one component of HHS's National Plan to Address Alzheimer's Disease, updated in April 2014 with input from numerous experts in aging and AD from Federal, State, private and non-profit organizations, as well as caregivers and people with the disease. As the lead agency in implementing Goal #1 of the National Plan to Prevent and Effectively Treat Alzheimer's Disease by 2025, NIH has adopted milestones to achieve a number of research objectives. NIH and many other Federal agencies have been active participants in Global Action Against Dementia (GAAD), a G7 effort launched in December 2013. In February 2015, NIH will host a research summit on Alzheimer's Disease that will include international participation and presentations, followed by a half-day meeting focused on G7 research tracking and collaborations. NIH's ability to identify new research opportunities and track research progress will be aided by these international collaborative efforts, including the IADRP. NIH will continue to work with its many partners until an effective treatment or cure can be found for this terrible disease. The request includes an additional $51 million for AD research in FY 2016, for an estimated total of $638 million.

**Theme 3: Harnessing Data and Technology to Improve Health**

Rapid expansion of technological capabilities has opened new horizons for biomedical research. Biomedical science continues to generate immense and complex datasets that present challenges for data creation, storage, and analysis, but also extraordinary opportunities to answer questions about biology, behavior, and medicine that previously were unanswerable. Innovative research methods stimulated by technological advances are facilitating the development of new strategies to diagnose, prevent, and treat a host of diseases. Technology also facilitates the integration of previously disparate fields, such as biology and electronics, enabling NIH to cultivate new lines of medical research and practice.

*Utilizing Technology to Combat Cancer*

Due in large part to advances in rapid sequencing technology, NIH-supported research is paving the way for individualized precision medicine in cancer treatment. Until recently, cancer treatments were limited to surgery, radiation, and chemotherapy, which all carry risks and typically lack the precision to attack only cancerous cells. New research strategies in which the therapy is optimized for a particular person based on key characteristics of their specific cancer cells holds the promise of a transformation in cancer treatment. NIH laid the foundation for these therapies by supporting The Cancer Genome Atlas (TCGA) to provide a comprehensive genomic analysis of many cancer types, and the continued success of the TCGA is due in large part to advances in rapid sequencing technology. Data generation and analysis for TCGA projects will continue into FY 2016, and the foundational datasets gathered through this research, as well as important methodological advances, will be applied to improve patient outcomes in the future.

For example, TCGA and other basic research has informed the development of targeted therapies for cancer, which use drugs to inhibit specific proteins on cancer cells that are linked to the behavior of those cells. In one instance, NIH-supported researchers developed a new technology

to analyze proteins on the surface of cancer cells that could be ideal targets for treatment. The new technology uses a highly sensitive method that requires just a few of a patient's cells and could eventually lead to determining which treatment will be most effective for each patient.

Named *Science* magazine's 2013 Breakthrough of the Year, another promising and rapidly developing treatment option driven by technology is cancer immunotherapy, which directs the patient's own immune system to attack cancer cells. In one approach, certain types of immune cells, called T-cells, are collected from cancer patients and engineered to produce special proteins on their surface. When these engineered T-cells are infused back into patients, they have the power to seek and destroy cancer cells. Initial trials of this type of therapy have been very successful, opening up new opportunities for cancer precision medicine.

*Applying the Microbiome*

Using powerful genomic sequencing technologies, researchers in 2012 reported the "healthy" human microbiome, which includes trillions of microbes (bacteria, fungi, and viruses). In 2007, NIH launched the Human Microbiome Project (HMP) with the goal of increasing understanding of the microbes living in and on the human body and their role in health and disease. More recent efforts focus on characterizing how the microbiome is related to specific diseases, creating the first integrated dataset of biological properties from both the microbiome and the host. These research efforts have generated more than 14 terabytes of sequencing data, highlighting not only the need for continued investment in this growing area of science, but also the need to augment NIH investments in data coordination and management systems.

By using these high-throughput multi-omics analyses (the collective characterization and quantification of different groups of biological molecules) to study the human microbiome, researchers are unearthing connections to diseases that could have a major impact on public health. For example, a study in mice that have features of autism spectrum disorder pointed to a possible link between the gut microbiome and autism. In this research, an oral treatment targeted at altering the microbiome resulted in improved behavior in the mice. A number of studies also have examined the role of the microbiome in obesity, uncovering a link between an increase in the amount of one kind of bacteria and a decrease in certain other bacteria depending on the subject's weight. The microbiomes of people with Type 2 Diabetes have distinct features as well, and additional research may uncover whether these differences play a role in causing the disease or if the differences are a result of the disorder, as well as lead to potential treatments.

*Big Data to Knowledge*

The computational needs for maintaining, securing, and processing large-scale digital datasets go far beyond the capabilities of individual investigators and even individual institutions. Biomedical Big Data can come in many forms – through the use of sophisticated technologies such as high-definition brain imaging, next-generation gene sequencing, and mHealth (mobile health) applications to track and improve health behaviors with the support of mobile devices, just to name a few. NIH is playing a major role in coordinating access to and analysis of the many types of biological and behavioral Big Data generated by biomedical scientists. To this end, NIH developed the Big Data to Knowledge (BD2K) Initiative in 2012 with the goal of establishing systems and expertise that enable optimal use of Big Data in biomedical science. NIH announced an initial investment of $32 million in BD2K awards in FY 2014, with projections for a total investment of over $600 million through 2020, pending available funds.

With the recent appointment of an Associate Director for Data Science at NIH, the BD2K program will expand in FY 2016 (by $19.5 million) and beyond.

The BD2K Initiative focuses on developing innovative and transformative approaches as well as tools to make Big Data and data science a prominent component of biomedical research. Funding opportunities concentrate on four major areas: enabling data utilization by the development of a Data Commons; analysis methods and software; enhancing training; and centers of excellence. For example, in FY 2016, NIH will support awards to train scientists at all career levels in Big Data science as well as for developing courses for skills development and open educational resources.

*Bioelectronic Medicine*

Advances in a range of biomedical science disciplines and coincident technology development have opened the door for NIH to support a new, high-risk, goal-driven research area. Bioelectronic medicine describes a newly forged field of "electroceuticals" that combines electronics and biology to treat a wide variety of diseases and conditions, by harnessing the powerful influence of the peripheral nervous system. In bioelectronic medicine, nano-scale electronic devices are connected to groups of nerve fibers, and then electrical impulses are used to stimulate the peripheral nerves throughout the body, the autonomic nervous system that regulates involuntary functions, and the enteric nervous system that controls the gastrointestinal system. With scientific advances that are mapping disease-specific neural circuits, bioelectronic medicine has the potential to control the function of physiologic systems and treat such conditions as hypertension and chronic pain.

NIH's new bioelectronic medicine program – Stimulating Peripheral Activity to Relieve Conditions (SPARC) – will develop proof-of-concept for an entirely new class of neural control devices that have the potential to restore health to organs and to ameliorate biological deficiencies. Using Other Transaction Authority (OTA), NIH will fund high-risk, discrete goal-focused, and milestone-driven research supported through the NIH Common Fund, as well as numerous Institutes and Centers. Basic research funded by NIH, including efforts to map the human brain, as well as to identify how particular nerves in the body relate to specific diseases, will inform significantly the field of bioelectronic medicine. Additionally, the program will support projects to establish precise and effective methods for administering electrical impulses to the nervous system. NIH anticipates spending $30 million for this program in FY 2016.

*National Patient-Centered Clinical Research Network*

Although mountains of health information are generated every day as part of routine visits between a patient and a physician, our capacity to study and compare clinical outcomes data from multiple clinical centers has been extremely limited. To address this issue, the non-governmental Patient-Centered Outcomes Research Institute (PCORI) launched PCORnet: the National Patient-Centered Clinical Research Network. PCORnet is a network of 11 clinical data research networks and 18 patient-powered research networks representing more than 100 million covered lives. PCORnet will harness the data from these networks to support clinical research in a large, highly representative network and provide much-needed answers to pressing clinical questions quickly and inexpensively. This research will be fully funded by PCORI .

In FY 2016, NIH will continue to expand its investments in observational and interventional comparative effectiveness trials using research networks such as the PCORnet platform.

PCORnet is unique in that it brings together patients, care providers, and health systems in partnerships to embed research into routine clinical practice in order to find out what treatments and health care practices work in the real world.

**Theme 4: Preparing a Diverse and Talented Biomedical Research Workforce**

Biomedical research can only advance and eventually produce the cures and treatments that improve human health if there is a workforce of diverse, well-trained, and highly creative people who can conduct this important work. NIH cultivates the human capital needed to fulfill its mission by providing training grants and fellowships to graduate students and postdoctoral researchers. In addition, NIH has taken steps to enhance diversity in the workforce and to prepare young scientists for careers in this dynamic field by equipping them with training that crosses sectors and disciplines.

Attracting and retaining creative individuals in the biomedical research workforce requires a stable funding environment and opportunities for career growth. Without this, young scientists and even well-established investigators may become discouraged and pursue other career options.

*Supporting Innovative Researchers and Transformative Research*

The pace of biomedical research is often perceived as slow, as researchers advance knowledge in an incremental process. The High-Risk High-Reward (HRHR) program, funded initially through the Common Fund, seeks to complement this process by supporting innovative investigators whose research goals are potentially transformative and would represent a significant leap ahead in scientific knowledge. Within this program, Pioneer Research Awards are available to investigators at any career stage; New Innovator Awards are for early-stage investigators; Transformative Research Awards are open to scientists at any career stage and are the only HRHR awards open to teams of investigators; and Early Independence Awards are open to exceptional junior scientists within one year of completing their terminal research degree or clinical residency. The HRHR program has led to hundreds of high-impact scientific discoveries and publications, patents, and enhanced collaboration. An evaluation of the Pioneer Award program has found that research conducted by Pioneer awardees is highly innovative, with a greater impact than traditional R01 grantees.[2]

In addition to those HRHR activities managed within or in collaboration with the NIH Common Fund, a number of NIH Institutes and Centers are now introducing similar programs of their own. The National Institute on Drug Abuse (NIDA) adopted the Pioneer award mechanism for its Avant Garde Award Program for HIV/AIDS Research, which supports highly creative scientists who propose novel approaches to HIV/AIDS research that also is relevant to drug abuse. The Biobehavioral Research Awards for Innovative New Scientists (BRAINS) funded by the National Institute of Mental Health (NIMH) helps exceptional, early-career scientists launch innovative research programs that have the potential to transform mental health research. The National Institute of Environmental Health Sciences (NIEHS) offers the Outstanding New Environmental Scientist (ONES) Award to inventive new scientists who are committed to advancing knowledge about the effect of environmental exposure on health. Other Institutes

[2] See: http://commonfund.nih.gov/pioneer/evaluations

adopting their own HRHR awards include the National Institute of General Medical Sciences, which plans to pilot the Maximizing Investigators' Research Award in FY 2016.

*Strengthening the Biomedical Research Workforce*

Technological advances and a new understanding of the vast complexity of biological and behavioral systems are moving biomedical research toward increasingly multidisciplinary work, in which individuals from many different sectors collaborate to ensure scientific progress. Non-traditional career paths also have become increasingly common as funding for academic research positions has leveled off and even declined. Given the changing research environment and unpredictable future, it is vital to equip young scientists with a range of skills and experiences, as was recommended by the Advisory Committee to the Director (ACD) Biomedical Research Workforce Working Group.[3] NIH has responded to these changes by giving graduate students and postdoctoral scientists exposure to career options in many different sectors. The Broadening Experiences in Scientific Training (BEST) Awards allow trainees to supplement their academic experience with training in industry, non-profits, government, policy, science communication, and other settings within the biomedical research enterprise. NIH created a Division of Biomedical Research Workforce Programs, including a Labor Economist charged with modeling the workforce, expanding NIH's understanding of workforce dynamics through economic analysis, and managing the Biomedical Research and Development Price Index. Using better analysis of the biomedical workforce and evaluation of NIH policies will enable NIH to align its programs and policies with workforce needs.

NIH also is committed to training physician-scientists, whose ability to bridge the lab and clinic is vital to translating scientific discoveries to clinical practices. However, the number of physician-scientists entering the biomedical research workforce has declined in recent years. To address this trend, NIH asked ACD to recommend actions NIH should take to support a sustainable and diverse physician-scientist workforce. ACD formed the Physician-Scientist Workforce Working Group to deliberate this topic, and the group studied the impact of various NIH training programs and considered major challenges that hinder entry into the workforce. In June 2014, the Working Group reported their recommendations for strengthening the training of physician-scientists, especially for those early in the pipeline.[4] Some of these recommendations included developing tools to better track training outcomes and career choices, grant mechanisms and award processes to support aspiring physician-scientists, pilot programs to test approaches to improve and/or shorten research training, and increasing efforts to diversify the physician-scientist workforce.

*Enhancing Diversity*

The biomedical workforce of the future should reflect the diversity of the public it serves. NIH strongly supports the goal of enhancing the diversity of the biomedical workforce and is taking steps to strengthen it by attracting the most talented individuals from all groups, with particular attention to the recruitment of individuals from economically disadvantaged and underrepresented backgrounds, as identified by the National Science Foundation.[5] To that end,

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[3] See: http://acd.od.nih.gov/Biomedical_research_wgreport.pdf
[4] See http://acd.od.nih.gov/reports/PSW_Report_ACD_06042014.pdf
[5] See http://www.nsf.gov/statistics/wmpd/2013/pdf/nsf13304_digest.pdf

NIH has taken a number of steps to foster diversity, including the appointment of a new NIH Chief Officer for Scientific Workforce Diversity in March 2014.

The Enhancing the Diversity of the NIH-Funded Workforce Program was established by NIH to provide individuals from underrepresented backgrounds with the support and tools necessary to participate in the biomedical workforce. Awarded in FY 2014, the program consists of three integrated initiatives that support a consortium of more than 50 investigators and partnering institutions who work together to develop and test new ways of training and mentoring young scientists. The Building Infrastructure Leading to Diversity (BUILD) Initiative is a set of experimental training awards designed to learn how to attract a diverse array of students into the training pipeline and to encourage their persistence to become future NIH-supported researchers. The 10 BUILD awardees will work with multiple partnering institutions with high concentrations of students from disadvantaged backgrounds to implement transformative, broad-based approaches to the training and mentoring of students to undertake biomedical research. The National Research Mentoring Network (NRMN) was established to increase access to high-quality research mentorship and networking opportunities by establishing a nationwide, interconnected set of skilled mentors linked to mentees from a variety of scientific disciplines, develop best practices for mentoring, provide training for mentors, as well as professional opportunities for mentees. Finally, the Coordinating and Evaluation Center (CEC) will rigorously evaluate BUILD and NRMN to determine the efficacy of new approaches being tested, facilitate the development of consortium-wide hallmarks of success, and serve as the focal point for dissemination of successful training and mentoring strategies.

NIH will continue to develop new ways to engage and sustain the interest of young scientists from underrepresented backgrounds with the goal of attracting them to careers in biomedical research. Achieving this goal will require NIH to share the strategies and tools young scientists need throughout the training process and at all career stages. Evaluations from CEC will provide the evidence for determining which approaches are successful, and results will be disseminated widely so that others can adopt these approaches.

## Conclusion

The Nation's investment in NIH, which funds biomedical researchers in every State across the country, has led to countless advances in the sciences of human health and disease. Each year, approximately 83 percent of NIH's budget is awarded through more than 60,000 research and research training grants to the Nation's finest institutions, small businesses, and scientists. Scientific and technological breakthroughs generated by NIH-supported research have fueled many of this country's gains in health and longevity. A child born today can look forward to an average lifespan of about 79 years - nearly three decades longer than a baby born in 1900.[6] Much of the recent improvement in death rates and life expectancy can be attributed to reductions in death rates from major causes of death, such as heart disease, cancer, stroke, and chronic lower respiratory diseases. Over the past 60 years, deaths from heart disease have fallen by more than 70 percent. Cancer death rates have been dropping more than 1 percent annually for the past 15 years (annual decline of 1.8 percent for men and 1.4 percent for women), resulting in life

[6] Xu J, Kochanek KD, Murphy SL, and Arias E. NCHS Data Brief: Mortality in the United States, 2012. Centers for Disease Control and Prevention. Oct 2014; Number 168. http://www.cdc.gov/nchs/data/databriefs/db168.htm

expectancy gains that are estimated to have saved the United States trillions of dollars.[7, 8] Likewise, HIV/AIDS treatments have extended lives greatly, and emerging strategies are enabling us to envision the first AIDS-free generation since this virus emerged more than 30 years ago. Federal Government funding contributed to the development of 48 percent of all drugs approved by the FDA and 65 percent of drugs that have received priority review between 1988 and 2005.[9]

NIH-funded research not only improves the health of Americans but also provides significant benefits to the U.S. economy. NIH research helps to reduce health care spending by producing better, more cost-effective therapies and preventive strategies. For example, a universal flu vaccine could reduce incidence and deaths significantly and potentially reduce the estimated $87.1 billion in annual medical costs, loss of lives, and lost productivity. NIH research also creates jobs and generates economic growth for the country. According to a report from United for Medical Research, in 2012, NIH funding supported more than 400,000 jobs across all 50 States and the District of Columbia.[10] In another independent analysis, Battelle's *2014 Global R&D Funding Forecast* states, "large research initiatives like the Human Genome Project or the War on Cancer...have high rates of social and economic return over the long term."[11] Battelle's *The Impact of Genomics on the U.S. Economy* describes the staggering economic return from genomics research: the $3.8 billion initial investment by the United States in the Human Genome Project (HGP) plus the additional $8.5 billion in HGP-related research and support has resulted in nearly $1 trillion of economic growth. Amazingly, the cost of this Federal funding, according to Battelle, is only $2 per year for each U.S. resident.[12]

Recognizing the large role that biomedical science plays in innovation and economic growth, many countries around the world have increased substantially their investment in biomedical science. While global investment in medical research is to be welcomed, as the largest funder of biomedical research in the world, NIH must continue to be a leader in this enterprise, supporting transformative basic, translational, and clinical research that will advance the health of the Nation, and preparing a highly creative and productive workforce to meet the major biomedical challenges of today and tomorrow.

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[7] Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975–2009, Featuring the Burden and Trends in HPV-Associated Cancers and HPV Vaccination Coverage Levels. *J Natl Cancer Inst*. 2013 Feb 6;105(3):175-201.

[8] Murphy KM and Topel RH. The Value of Health and Longevity. *Journal of Political Economy*, 2006, 114(5).

[9] Sampat BN, Lichtenberg FR. What are the respective roles of the public and private sectors in pharmaceutical innovation? *Health Affairs*. 2011; 30:332-339.

[10] United for Medical Research. 2012. *NIH's Role in Sustaining the U.S. Economy*. http://www.unitedformedicalresearch.com/wp-content/uploads/2012/07/NIHs-Role-in-Sustaining-the-US-Economy-2011.pdf

[11] Battelle and R&D Magazine. 2013. *2014 Global R&D Funding Forecast*. http://www.battelle.org/docs/tpp/2014_global_rd_funding_forecast.pdf?sfvrsn=4

[12] Battelle. 2013. *The Impact of Genomics on the U.S. Economy*. http://web.ornl.gov/sci/techresources/Human_Genome/publicat/2013BattelleReportImpact-of-Genomics-on-the-US-Economy.pdf

## IMPACT OF BUDGET LEVEL ON PERFORMANCE

| Programs and Measures (Dollars in Millions, except where noted) | FY 2015 Enacted[1] | FY 2016 President's Budget | FY 2016 +/- FY 2015 |
|---|---|---|---|
| Research Project Grants | $16,332.639 | $17,205.659 | 5.3% |
| Competing Average Cost (in thousands) | $457.312 | $460.696 | 0.7% |
| Number of Competing Awards (whole number) | 9,076 | 10,303 | 13.5% |
| Estimated Competing RPG Success Rate (absolute rate) | 17.2% | 19.3% | 12.4% |
| Research Centers | $2,699.292 | $2,636.643 | -2.3% |
| Other Research | $1,844.207 | $1,882.049 | 2.1% |
| Training | $762.071 | $785.483 | 3.1% |
| Research & Development Contracts | $2,898.740 | $2,895.964 | -0.1% |
| Intramural Research | $3,425.860 | $3,520.574 | 2.8% |
| Research Management and Support | $1,560.897 | $1,580.442 | 1.3% |
| *Common Fund (non-add)* | *$545.639* | *$565.639* | *3.7%* |
| Buildings & Facilities Appropriation | $128.863 | $128.863 | 0.0% |
| Other Mechanisms[2] | $658.779 | $675.673 | 2.6% |
| **Total, Program Level[3]** | **$30,311.349** | **$31,311.349** | 3.3% |

[1] Excludes Ebola-related funding.

[2] Includes Office of the Director-Other, building repair & improvement (R&I) funds allocated for the NCI-Frederick facility, and Superfund Research activities funded from the Interior appropriation.

[3] Includes discretionary budget authority received from Labor/HHS appropriations (ICs) and the Interior appropriation (Superfund). Also includes mandatory budget authority derived from the Special Type 1 Diabetes account, and Program Evaluation Financing.

## OVERVIEW OF PERFORMANCE

The NIH mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. 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 2016 budget request reflects the Agency's longstanding commitment to invest strategically using performance-based analysis, as emphasized in the GPRA Modernization Act of 2010 (P.L. 111-352). Through the continuous evaluation and strategic management of its research portfolio, NIH focuses on funding research that shows the greatest promise for improving the overall health of the American people. In addition, NIH continually seeks to identify and address high-priority scientific opportunities and emerging public health needs. By managing its research portfolio to support key research priorities, NIH ensures the most effective use of funds to achieve the greatest impact on the health and welfare of the Nation. In particular, NIH's strong peer-review process, site visits, performance monitoring, program evaluation, and performance-based contracting enable the Agency to ensure that its investments generate results for the American people.

NIH strives to achieve transparency and accountability by regularly reporting results, achievements, and the impact of its activities. To increase transparency and promote effective use of resources, NIH began reporting the amount of indirect costs paid per grant on its Research Portfolio Online Reporting Tools website (NIH RePORT) in October 2013. NIH 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, NIH uses a set of performance measures that is representative of its activities and is useful for tracking progress in achieving performance priorities. This representative approach has helped 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. In this request, NIH is proposing 45 new measures to replace those that ended or will be ending soon. The development of the new measures was coordinated by the Office of the Director (OD), which identified gaps in the NIH's performance measure portfolio, and sought input from all 27 Institutes and Centers (ICs), as well as key offices within OD, to fill these gaps. A multi-level review process, supported by two trans-NIH committees, was used to develop, refine, and select measures that best align with the Agency's performance priorities. All of NIH's measures also support the goals and objectives of the HHS Strategic Plan 2014-2018. In particular, NIH substantially contributes to the HHS Strategic Goal 2–Advance Scientific Knowledge and Innovation. For example, in FY 2016, in support of Objective A (Accelerate the process of scientific discovery to improve health) under Goal 2, NIH will support promising biomedical research and human capital investment with the goals of: 1) identifying two molecular-targeted therapies for disorders of the immune system in

children, and 2) providing research training for predoctoral trainees and fellows as well as postdoctoral fellows to promote greater retention and long-term success in research careers.

**Performance Management**

Performance management at 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 ICs and OD. OD is the central office responsible for setting policy for 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 toward 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 obstacles 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 international entities. Joint research and training activities and other exchanges with such groups increase the leverage of NIH resources and support vibrant partnerships to help NIH achieve its mission. 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 process. For example, the Extramural Research Program, which includes 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 ICs. For the Intramural Research Program, the progress of individual scientists and their laboratories is evaluated once every four 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 NIH maintains 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 Committee and seven standing Working Groups.[13,14] 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, NIH can maximize its perspective and expertise in the development and oversight of policies common to 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 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 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 NIH to make critical adjustments periodically to align activities and target resources in support of its research priorities.

[13] 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.

[14] The seven standing working groups are: Extramural Activities, Diversity, Facilities, Management and Budget, Scientific Data Council, Administrative Data Council, and Clinical Center Governing Board.

## BUDGET BY HHS STRATEGIC OBJECTIVE

| (Dollars in Millions) | FY 2014 Actual | FY 2015 Enacted[1] | FY 2016 President's Budget |
|---|---|---|---|
| **1.Strengthen Health Care** | | | |
| 1.A Make coverage more secure for those who have insurance, and extend affordable coverage to the uninsured | | | |
| 1.B Improve health care quality and patient safety | | | |
| 1.C Emphasize primary and preventive care, linked with community prevention services | | | |
| 1.D Reduce the growth of health care costs while promoting high-value, effective care | | | |
| 1.E Ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations | | | |
| 1.F Improve health care and population health through meaningful use of health information technology | | | |
| **2. Advance Scientific Knowledge and Innovation** | **29,934** | **30,174** | **31,166** |
| 2.A Accelerate the process of scientific discovery to improve health | 29,934 | 30,174 | 31,166 |
| 2.B Foster and apply innovative solutions to health, public health, and human services challenges | | | |
| 2.C Advance the regulatory sciences to enhance food safety, improve medical product development, and support tobacco regulation | | | |
| 2.D Increase our understanding of what works in public health and human services practice | | | |
| 2.E Improve laboratory, surveillance, and epidemiology capacity | | | |
| **3. Advance the Health, Safety and Well-Being of the American People** | | | |
| 3.A Promote the safety, well-being, resilience, and healthy development of children and youth | | | |
| 3.B Promote economic and social well-being for individuals, families, and communities | | | |
| 3.C Improve the accessibility and quality of supportive services for people with disabilities and older adults | | | |
| 3.D Promote prevention and wellness across the life span | | | |
| 3.E Reduce the occurrence of infectious diseases | | | |
| 3.F Protect Americans' health and safety during emergencies, and foster resilience to withstand and respond to emergencies | | | |
| **4. Ensure Efficiency, Transparency, Accountability, and Effectiveness of HHS Programs** | **136** | **137** | **145** |
| 4.A Strengthen program integrity and responsible stewardship by reducing improper payments, fighting fraud, and integrating financial, performance, and risk management | | | |
| 4.B Enhance access to and use of data to improve HHS programs and to support improvements in the health and well-being of the American people | | | |
| 4.C Invest in the HHS workforce to help meet America's health and human services needs | | | |
| 4.D Improve HHS environmental, energy, and economic performance to promote sustainability | 136 | 137 | 145 |
| **TOTAL** | **30,070** | **30,311** | **31,311** |

[1] Excludes Ebola-related funding.

# BUDGET MECHANISM TABLE

| (Dollars in Thousands) [1, 2] | FY 2014 Actual | | FY 2015 Enacted[7] | | FY 2016 President's Budget | | FY 2016 +/- FY 2015 | |
|---|---|---|---|---|---|---|---|---|
| | No. | Amount | No. | Amount | No. | Amount | No. | Amount |
| Research Projects: | | | | | | | | |
| Noncompeting | 23,504 | $10,785,361 | 23,433 | $11,294,016 | 23,303 | $11,524,971 | -130 | $230,955 |
| Administrative Supplements | *(1,588)* | 208,245 | *(1,479)* | 172,045 | *(1,420)* | 168,834 | *(-59)* | -3,212 |
| Competing: | | | | | | | | |
| Renewal | 1,897 | 1,297,091 | 2,049 | 1,062,346 | 2,264 | 1,143,837 | 215 | 81,491 |
| New | 7,223 | 3,167,751 | 6,987 | 3,078,440 | 7,996 | 3,592,077 | 1,009 | 513,637 |
| Supplements | 48 | 14,318 | 40 | 9,781 | 43 | 10,641 | 3 | 859 |
| Subtotal, Competing | 9,168 | $4,479,160 | 9,076 | $4,150,567 | 10,303 | $4,746,555 | 1,227 | $595,988 |
| Subtotal, RPGs | 32,672 | $15,472,767 | 32,509 | $15,616,627 | 33,606 | $16,440,359 | 1,097 | $823,732 |
| SBIR/STTR | 1,660 | 695,480 | 1,697 | 716,012 | 1,841 | 765,300 | 144 | 49,288 |
| Research Project Grants | 34,332 | $16,168,247 | 34,206 | $16,332,639 | 35,447 | $17,205,659 | 1,241 | $873,020 |
| Research Centers: | | | | | | | | |
| Specialized/Comprehensive | 1,117 | $1,958,143 | 1,130 | $1,929,147 | 1,171 | $1,894,298 | 41 | -$34,849 |
| Clinical Research | 60 | 413,671 | 60 | 416,824 | 60 | 411,742 | | -5,082 |
| Biotechnology | 93 | 167,045 | 94 | 165,694 | 99 | 152,972 | 5 | -12,722 |
| Comparative Medicine | 51 | 129,353 | 52 | 131,500 | 49 | 122,254 | -3 | -9,246 |
| Research Centers in Minority Institutions | 22 | 55,067 | 21 | 56,127 | 20 | 55,377 | -1 | -750 |
| Research Centers | 1,343 | $2,723,280 | 1,357 | $2,699,292 | 1,399 | $2,636,643 | 42 | -$62,650 |
| Other Research: | | | | | | | | |
| Research Careers | 3,624 | $611,866 | 3,632 | $614,794 | 3,648 | $619,919 | 16 | $5,125 |
| Cancer Education | 96 | 32,932 | 96 | 32,932 | 96 | 32,738 | | -195 |
| Cooperative Clinical Research | 394 | 474,587 | 385 | 468,828 | 386 | 503,987 | 1 | 35,160 |
| Biomedical Research Support | 111 | 67,391 | 105 | 64,579 | 105 | 64,579 | | |
| Minority Biomedical Research Support | 287 | 104,470 | 283 | 103,115 | 282 | 102,920 | -1 | -195 |
| Other | 1,722 | 555,627 | 1,689 | 559,959 | 2,010 | 557,907 | 321 | -2,053 |
| Other Research | 6,234 | $1,846,873 | 6,190 | $1,844,207 | 6,527 | $1,882,049 | 337 | $37,842 |
| Total Research Grants | 41,909 | $20,738,399 | 41,753 | $20,876,138 | 43,373 | $21,724,351 | 1,620 | $848,213 |
| Ruth L. Kirchstein Training Awards: | FTTPs | | FTTPs | | FTTPs | | FTTPs | |
| Individual Awards | 3,058 | $136,141 | 3,105 | $140,036 | 3,234 | $146,846 | 129 | $6,810 |
| Institutional Awards | 12,258 | 602,287 | 12,426 | 622,034 | 12,501 | 638,636 | 75 | 16,602 |
| Total Research Training | 15,316 | $738,429 | 15,531 | $762,071 | 15,735 | $785,483 | 204 | $23,412 |
| Research & Develop. Contracts | 2,211 | $2,990,140 | 2,078 | $2,898,740 | 2,095 | $2,895,964 | 17 | -$2,777 |
| *(SBIR/STTR) (non-add)* | *(115)* | *(65,426)* | *(129)* | *(73,771)* | *(132)* | *(78,580)* | *(3)* | *(4,810)* |
| Intramural Research | 7,060 | $3,384,285 | 7,087 | $3,425,860 | 7,080 | $3,520,574 | -7 | $94,714 |
| Res. Management & Support | 5,574 | 1,527,790 | 5,624 | 1,560,897 | 5,631 | 1,580,442 | 7 | 19,544 |
| *(SBIR Administrative) (non-add)* | *(3)* | *(3,687)* | *(30)* | *(4,054)* | *(0)* | *(0)* | *(-30)* | *(-4,054)* |
| *Office of the Director - Appropriation* [3] | | *(1,303,014)* | | *(1,413,734)* | | *(1,442,628)* | | *(28,894)* |
| Office of the Director - Other | | 477,354 | | 573,430 | | 582,324 | | 8,894 |
| *ORIP/SEPA (non-add)* [3] | | *(294,486)* | | *(294,665)* | | *(294,665)* | | *(0)* |
| *Common Fund (non-add)* [3] | | *(531,174)* | | *(545,639)* | | *(565,639)* | | *(20,000)* |
| Buildings and Facilities[4] | | 136,316 | | 136,863 | | 144,863 | | 8,000 |
| *Appropriation* | | *(128,663)* | | *(128,863)* | | *(128,863)* | | *(0)* |
| Type 1 Diabetes[5] | | -139,200 | | -150,000 | | -150,000 | | 0 |
| Program Evaluation Financing[6] | | -8,200 | | -715,000 | | -847,489 | | -132,489 |
| **Subtotal, Labor/HHS Budget Authority** | | **$29,845,313** | | **$29,369,000** | | **$30,236,511** | | **$867,511** |
| Interior Appropriation for Superfund Research | | 77,349 | | 77,349 | | 77,349 | | 0 |
| **Total, NIH Discretionary Budget Authority** | | **$29,922,662** | | **$29,446,349** | | **$30,313,860** | | **$867,511** |
| Type 1 Diabetes | | 139,200 | | 150,000 | | 150,000 | | 0 |
| **Total, NIH Budget Authority** | | **$30,061,862** | | **$29,596,349** | | **$30,463,860** | | **$867,511** |
| Program Evaluation Financing | | 8,200 | | 715,000 | | 847,489 | | 132,489 |
| **Total, Program Level** | | **$30,070,062** | | **$30,311,349** | | **$31,311,349** | | **$1,000,000** |

[1] All Subtotal and Total numbers may not add due to rounding.
[2] All numbers in italics and brackets are non-add.
[3] 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 the remaining funds are accounted
[4] Includes B&F appropriation and funds for facilities repairs and improvements at the NCI Federally Funded Research and Development Center in Frederick, Maryland.
[5] 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.
[6] Number of grants and dollars for Program Evaluation Financing are distributed by mechanism above; therefore, the amount is deducted to provide subtotals only for the Labor/HHS Budget Authority.
[7] Excludes Ebola related funding.