

**PREPARED STATEMENT OF LAWRENCE A. TABAK, D.D.S., Ph.D.
PRINCIPAL DEPUTY DIRECTOR, OFFICE OF THE DIRECTOR**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the Office of the Director (OD) of the National Institutes of Health (NIH).

The OD promotes and fosters NIH research and research training efforts in the prevention and treatment of disease through the policy oversight of both the extramural grant and contract award functions, the Intramural Research program, and through the coordinating efforts of several cross-cutting program offices responsible for stimulating specific areas of research throughout NIH to complement the ongoing efforts of the Institutes and Centers. The OD also develops policies in response to emerging scientific opportunities employing ethical and legal considerations; coordinates the communication of health information to the public and scientific communities; provides oversight and management of peer review policies; and coordinates information technology across NIH. The OD also provides the core administrative and management services, such as budget, human resources, property management, procurement services, ethics oversight, committee management, and the administration of equal employment policies and practices.

The FY 2019 budget request will also support activities managed by the OD's operational offices. The OD Operations is comprised of several OD Offices that provide advice to the NIH Director, policy direction and oversight to the NIH research community, and administer centralized support services essential to the NIH mission. In addition to the Common Fund (CF) administered by the Division of Program Coordination, Planning, and Strategic Initiatives, two additional research programs, Environmental Influences on Child Health Outcomes (ECHO) and the All of Us Research Program, are coordinated within the OD. The functions and initiatives of the OD's research offices and programs are described in detail as follows:

**DIVISION OF PROGRAM COORDINATION, PLANNING,
AND STRATEGIC INITIATIVES (DPCPSI)**

DPCPSI provides leadership for identifying, reporting, and funding trans-NIH research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that merit further research and would benefit from collaboration between two or more ICs, or from strategic coordination and planning.

DPCPSI includes major programmatic offices that coordinate, and support research and activities related to HIV/AIDS, women's health, behavioral and social sciences, disease prevention, dietary supplements, and research infrastructure. DPCPSI serves as a resource for the ICs and OD for portfolio analysis by developing, using, and disseminating data-driven approaches and computational tools. DPCPSI serves as the focal point for coordinating research to advance the health and wellbeing of sexual and gender minorities and for American Indians and Alaska Natives, and coordinating tribal consultation activities for the NIH.

The Office of Research Infrastructure Program (ORIP) provides support for research into model systems of human diseases and a variety of research infrastructure needs. ORIP supports

a number of repositories of animal models, biological materials, genetic stocks, and human biospecimens. ORIP also makes grant awards to fund the purchase of expensive state-of-the-art scientific instruments and to update animal research facilities. ORIP supports training and career development for veterinarian-scientists engaged in biomedical research and contributing to interdisciplinary research teams addressing topics at the intersection of human/animal populations and the environment.

The Office of Aids Research (OAR) plays a unique role at NIH by serving as a model of trans-NIH planning and management, vested with primary responsibility for overseeing all HIV/AIDS-related research supported by the NIH. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH HIV/AIDS research program. OAR's response to the HIV/AIDS epidemic requires a unique and complex multi-institute, multi-disciplinary, global research program. This diverse research portfolio demands an exceptional level of scientific coordination and management of research funds to identify the highest-priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently.

The Office of Behavioral and Social Sciences Research (OBSSR) furthers the mission of the NIH by emphasizing the critical role that behavioral and social factors play in health, health care and well-being. OBSSR serves as a liaison between NIH and the extramural research communities, other Federal agencies, academic and scientific societies, national voluntary health agencies, the media, and the general public on matters pertaining to behavioral and social sciences research. OBSSR's vision is to bring together the biomedical, behavioral, and social science communities to work more collaboratively to solve the pressing health challenges facing our nation. OBSSR also coordinates and helps support the NIH Basic Behavioral and Social Science Opportunity Network, a trans-NIH initiative to expand the agency's funding of basic behavioral and social sciences research.

The Office of Research on Women's Health (ORWH) has worked to ensure the inclusion of women in NIH clinical research, to advance and expand women's health research, and to promote advancement of women in biomedical careers. ORWH is the focal point for NIH women's health research and works in partnership with the NIH ICs to incorporate a women's health and sex differences research perspective into the NIH scientific framework. ORWH activities are guided by the NIH Strategic Plan for Women's Health Research. This strategic plan outlines six goals to maximize impact of NIH research effort. The NIH strategic plan for women's health and sex differences research serves as a framework for interdisciplinary scientific approaches.

The Office of Disease Prevention (ODP) is responsible for assessing, facilitating, and stimulating research in disease prevention and health promotion, and disseminating the results of this research to improve public health. In FY 2019, ODP will release a new strategic plan which outlines the priorities that the Office will focus on over the next five years and highlights ODP's role in advancing prevention research at the NIH. The Office of Dietary Supplements (ODS) is within the ODP organizational structure. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and

supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

The Office of Strategic Coordination (OSC) and the Common Fund (CF)- OSC manages the Common Fund (CF), which functions as a “venture capital” space where high-risk, innovative endeavors with the potential for extraordinary impact can be supported. CF supports approximately 30 programs that focus on areas of emerging scientific opportunities, rising public health challenges, and knowledge gaps that deserve special emphasis; that would benefit from strategic coordination and planning across NIH Institutes and Centers (ICs); and that are designed to address specific, high-impact goals and milestones within a 5- to 10-year timeframe. Collectively, these programs represent strategic investments aimed at solving problems or building resources to affect research throughout the entire biomedical research enterprise. Most CF programs consist of a series of integrated initiatives that collectively address a set of goals aiming to transform the way research is conducted, the way that health and disease are understood, and/or the way that diseases are diagnosed or treated.

ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES

Launched in FY 2016, the Environmental Influences on Child Health Outcomes (ECHO) program supports multiple synergistic, longitudinal studies by leveraging, harmonizing, and combining existing and new data from 83 maternal/pediatric cohorts to create one ECHO-wide Cohort with 50,000 participants. Researchers will investigate the effects of a broad range of early life environmental exposures (e.g., physical/chemical, societal, psychosocial, behavioral, biological) on five key pediatric outcomes with high public health impact: pre-, peri-, and postnatal outcomes; upper and lower airway conditions; obesity; neurodevelopment and positive health.

The intervention component of ECHO is the IDeA States Pediatric Clinical Trials Network, with a goal to provide access for rural and medically underserved children to participate in state-of-the-art clinical trials. This network builds institutional capacity, provides professional development to researcher and their teams, and leverages partnerships with outside academic institutions. In FY 2019, having built its infrastructure, ECHO Cohorts will disseminate research findings, and the IDeA States Pediatric Network will continue to conduct one or more clinical trials.

ALL OF US RESEARCH PROGRAM

The *All of Us* Research Program, launched in FY 2016, is an ambitious effort to gather data on the biological, environmental, and behavioral influences on health and disease over many years from one million or more people living in the United States. *All of Us* will serve as a national research resource to inform thousands of studies, covering a wide variety of health conditions and enabling individualized prevention and treatment options for patients.

Since July 2016, *All of Us* achieved several key implementation milestones, including initial study protocol approval, establishment of a state-of-the-art biobank to process and store biological samples from patients, and construction of a big data IT system to store data for research purposes. Working together with a consortium of federal, academic, and industry partners, *All of Us* began participant enrollment for its beta testing phase in May 2017, and, as of

March 25, 2018, more than 35,000 participants are currently enrolled, of whom over 20,000 have completed the full protocol.

The program will begin full-scale, nationwide participant enrollment in the spring of 2018.

Lawrence A. Tabak, DDS, Ph.D.

Dr. Tabak is the Principal Deputy Director of the National Institutes of Health (NIH) and the Deputy Ethics Counselor of the Agency. He previously served as the Acting Principal Deputy Director of NIH (2009), and prior to that as Director of the National Institute of Dental and Craniofacial Research from 2000-10.

Dr. Tabak has provided leadership for numerous trans-NIH activities, including the NIH Roadmap effort to support team science, now known as the NIH Common Fund; the NIH Director's initiative to enhance peer review; NIH's American Recovery and Reinvestment Act implementation; the NIH initiative to enhance rigor and reproducibility in research; and the NIH-Wide Strategic Plan. He co-chaired working groups of the Advisory Committee to the Director of NIH (ACD) on the Diversity of the Biomedical Research Workforce and the Long-Term Intramural Research Program (LT-IRP) Planning, and currently co-chairs working groups of the ACD on the Next Generation of Investigators Initiative, High Risk/High Reward research, and the MACH trial.

Prior to joining NIH, Dr. Tabak was the Senior Associate Dean for Research and Professor of Dentistry and Biochemistry & Biophysics in the School of Medicine and Dentistry at the University of Rochester in New York. A former NIH MERIT recipient, Dr. Tabak's major research focus has been on the structure, biosynthesis and function of glycoproteins. He continues work in this area, maintaining an active research laboratory within the NIH intramural program in addition to his administrative duties. He is an elected member the National Academy of Medicine of the National Academies.

**PREPARED STATEMENT OF ROGER I. GLASS, M.D.
DIRECTOR, FOGARTY INTERNATIONAL CENTER**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the Fogarty International Center (FIC) of the National Institutes of Health (NIH).

INTRODUCTION

The idea that the U.S. could benefit from international collaborative research was central to the creation of the Fogarty International Center in 1968. Fogarty's namesake, Rhode Island Congressman John E. Fogarty, foresaw that U.S. citizens would reap the benefits of international discoveries and that global health was a smart investment for the U.S. and the world. Fifty years later, Congressman Fogarty's vision remains a guiding force as Fogarty continues to provide leadership in strengthening the research workforce here and abroad to ensure that the best and brightest minds are harnessed solve complex health challenges that affect us all.

Well-trained scientists have never been more critical to protecting the health of Americans and populations around the world. Infectious diseases like Ebola and Zika have traveled across borders, and diseases formerly found only in other countries are now present in the U.S. Therefore, it is imperative that we train scientists in developing countries to detect pandemics at their point of origin, contain outbreaks, and minimize their impact. In addition, the ability to collaborate with scientists abroad can generate valuable knowledge about diseases such as Alzheimer's Disease and cancer.

Fogarty supports research and research training programs for U.S. and low- and middle-income country (LMIC) scientists. These programs are built on long-standing partnerships between U.S. and LMIC academic institutions. Fogarty programs also extend the reach and competitiveness of U.S. universities, where there is high demand for international research opportunities. Currently, Fogarty supports over 500 research and training programs involving 100 universities. Roughly 80 percent of Fogarty grants are awarded to U.S. institutions and all Fogarty awards involve U.S. researchers.

STRENGTHEN AND SUSTAIN THE BIOMEDICAL WORKFORCE

Global Health Security: Emerging epidemics such as Ebola demand a critical mass of in-country scientists with relevant research expertise and skills. In 2016, Fogarty initiated the Emerging Epidemic Virus Research Training for West African Countries with Widespread Transmission of Ebola program. These grants fund collaborations between U.S. and African research institutions in Guinea, Liberia, and/or Sierra Leone to plan capacity building programs for Fogarty's Global Infectious Disease Research Training Program, with a focus on emerging viral epidemics. This support enables scientists on the front lines in these countries, which were ground zero for Ebola, to design training programs that increase expertise in Ebola, Lassa fever, and other emerging viral diseases. For example, Yale University, in partnership with the University of Liberia, will develop a training program focusing on predictive transmission modeling and epidemiological research. Fogarty has also awarded a grant to Tulane University,

the Vanderbilt Institute for Global Health, and the University of Sierra Leone. Together, these institutions will advance research focused on efficacy studies of novel and existing therapeutics for endemic viral hemorrhagic fevers like Lassa fever, while simultaneously building capacity on how to conduct higher-level clinical trial research during an epidemic like Ebola.

An in-house team of Fogarty-supported scientists develop and use advanced computational models to study the emergence, evolution, and transmission of pathogens to help predict future pandemics, provide actionable information early in outbreaks, and protect the U.S. population from these threats. For example, these researchers and their collaborators recently modeled the global migration of Zika virus and their potential for causing large outbreaks in the U.S. They have also studied the transmission dynamics and evolution of influenza viruses in humans, domestic animals, and migratory birds to help predict future pandemics.

Combatting Common Disease Threats. Fogarty also supports training of scientists in LMICs, many of whom have become leaders in academic institutions and ministries of health in their home countries and serve as critical partners for U.S. scientists. Notably, many health challenges facing Americans are most effectively addressed through research conducted in a global context, where diseases are often highly prevalent or where the study of unique genetic predispositions can inform how we detect and prevent certain diseases that affect U.S. citizens.

HIV/AIDS. Key scientific discoveries in HIV/AIDS treatment and prevention have been made by Fogarty-supported trainees and former trainees, including interventions to reduce mother-to-child transmission of HIV, using HIV treatment to prevent new HIV infections, and novel approaches to address HIV/TB coinfection. Fogarty-trained scientists in South Africa are now studying broadly neutralizing antibodies, which can kill multiple strains of the virus that causes AIDS. Produced by only about 20 percent of people with HIV, these antibodies show up too late to be able to stop disease progression in the people who make them. However, scientists are exploring their potential to prevent HIV in others - either through a vaccine that would coax the body to generate similar types of antibodies or via passive immunization in which an antibody product would be given directly.

Alzheimer's Disease. Columbia is home to the largest known family with an inherited, early-onset form of Alzheimer's. Testing new therapies on healthy individuals who are at a high risk for the disease, like those in this family, is providing valuable clues for understanding how to prevent it. Members of this family are now participating in a trial to determine if a drug provided by a U.S.-based company can stave off the decline in memory and brain function associated with the disease. Fogarty-supported research training helped to build a strong neuroscience research community in Colombia, which set the stage for this potentially game-changing research.

RESEARCH

Brain Disorders. Fogarty's Global Brain and Nervous Systems Disorders Research across the Lifespan Program supports cutting-edge research in LMICs on nervous system development, function, and impairment throughout life. The program allows U.S. investigators to gain experience working in LMICs, expanding the research workforce in these settings by

developing long-lasting international partnerships. This research network spans over 45 countries and has contributed to the creation of new interventions, new tools for clinical assessment, and new laboratory methods.

Hydrocephalus – excessive accumulation of fluid in the brain – is one of the most common birth defects in the U.S. The traditional treatment for hydrocephalus is the surgical placement of a shunt, which often involves complications like mechanical failure, obstruction, and infection. Global Brain-supported researchers working in Uganda developed a new treatment for infant hydrocephalus. They combined endoscopic third ventriculostomy and choroid plexus cauterization (ETV/CPC) into one treatment, where a small hole drains fluid from the brain and heat is applied to brain tissue to reduce fluid production. Both procedures have been practiced separately, but scarce resources in Uganda inspired researchers to combine the two practices. This combination treatment has helped to avoid shunt dependence in most Ugandan infants treated for this condition. Notably, ETV/CPC is now being practiced in the U.S.

Influenza. The Multinational Influenza Seasonal Mortality Study (MISMS) is an international effort led by FIC to model the epidemiology and evolutionary dynamics of influenza in human, swine and avian populations. With funding from DHHS since 2007, MISMS has developed a network of over three-hundred influenza experts in forty-five countries and studied a broad range of topics, including: the global circulation of influenza virus; cross-species transmission; pandemic preparedness; control strategies; transmission dynamics; historical pandemics; disease burden; and seasonality.

Mobile Health. Mobile technologies present exceptional opportunities and new tools for improving health outcomes. A mobile health tool conceived by a Fogarty grantee for HIV patient care in Uganda is now being used to help patients use their phones to adhere to strict medication regimen at a lower cost for conditions like opioid addiction, tuberculosis, and hepatitis C. Fogarty-supported researchers from the U.S. and Zambia are developing a simple diagnostic test for malaria that uses a few drops of blood and tiny magnetic beads to accurately detect the parasite that causes the disease. This new, inexpensive test improves malaria detection and reduces drug resistance by treating only those who have the disease.

CONCLUSION

Fogarty investments are enabling researchers to take science to where the problems are most acute, conduct research, and develop solutions in the places where diseases are especially challenging. This is the unique niche that Fogarty will continue to fill in FY 2018 and beyond.

Roger I. Glass, M.D.
Director, Fogarty International Center

Dr. Glass was named Director of the Fogarty International Center and Associate Director for International Research by NIH Director Elias A. Zerhouni, M.D., on March 31, 2006.

Dr. Glass graduated from Harvard College in 1967, received a Fulbright Fellowship to study at the University of Buenos Aires in 1967, and received his M.D. from Harvard Medical School and his M.P.H. from the Harvard School of Public Health in 1972. He joined the Centers for Disease Control and Prevention in 1977 as a medical officer assigned to the Environmental Hazards Branch. He was a Scientist at the International Center for Diarrheal Disease Research in Bangladesh from 1979-1983 and returned to Sweden where he received his doctorate from the University of Goteborg. In 1984, he joined the National Institutes of Health Laboratory of Infectious Diseases, where he worked on the molecular biology of rotavirus. In 1986, Dr. Glass returned to the CDC to become Chief of the Viral Gastroenteritis Unit at the National Center for Infectious Diseases.

Dr. Glass's research interests are in the prevention of gastroenteritis from rotaviruses and noroviruses through the application of novel scientific research. He has maintained field studies in India, Bangladesh, Brazil, Mexico, Israel, Russia, Vietnam, China and elsewhere. His research has been targeted toward epidemiologic studies to anticipate the introduction of rotavirus vaccines. He is fluent and often lectures in five languages.

Dr. Glass has received numerous awards including the prestigious Charles C. Shepard Lifetime Scientific Achievement Award presented by the CDC in recognition of his 30-year career of scientific research application and leadership, and the Dr. Charles Merieux Award from the National Foundation for Infectious Diseases for his work on rotavirus vaccines in the developing world. Dr. Glass is also the recipient of the 2015 Albert B. Sabin Gold Medal Award. He is a member of the National Academy of Medicine of the National Academies. Dr. Glass has co-authored more than 600 research papers and chapters.

He is married to Barbara Stoll, M.D., the H. Wayne Hightower Distinguished Professor in the Medical Sciences and Dean of the University of the Texas Medical School at Houston, and the father of three children: Nina, Michael and Andy Glass.

**PREPARED STATEMENT OF CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR,
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health.

NCATS is dedicated to understanding and transforming *translation*, defined as the process of turning scientific, medical, and public health observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public. At a time of unprecedented science discoveries, our collective ability to translate research findings into health benefits often is too slow and ineffective. Developing a new drug requires on average 10 to 15 years and more than \$2 billion given the high prevalence of failure along the translational pipeline. We must deliver the promise of science to patients in an accelerated and more efficient manner. NCATS studies and supports translation on a system-wide level as a scientific and operational problem, addressing roadblocks that impede or preclude promising advances.

Accelerating Clinical Translation

The largest portion of NCATS' budget is dedicated to its Clinical and Translational Science Awards (CTSA) Program. Through this program, NCATS supports a national network of medical research centers, called hubs, that collaborate locally, regionally, and nationally to foster innovation in clinical researcher training, patient engagement, and new research tools and processes. There are multiple initiatives within this program, including the Trial Innovation Network that is composed of the hubs as well as Trial Innovation Centers and a Recruitment Innovation Center. Through this network, researchers are identifying and implementing ways to improve the clinical trial process, including participant recruitment and other aspects of clinical trial conduct.

The process of obtaining ethics approval from multiple institutional review boards (IRBs) to conduct a clinical research study at multiple institutions is a longstanding challenge that can lead to significant delays in study activation. To address this problem, NCATS supported the development of a single IRB reliance platform for multisite clinical studies, enabling study sites to rely on a single IRB of record. The platform, known as the Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB, includes resources such as umbrella agreements, guidance documents, and consultation services that investigators nationwide can access to harmonize and streamline IRB review for their own multisite studies. SMART IRB is serving as a roadmap to help implement the NIH policy released in June 2016 that requires all NIH-funded multisite clinical studies to use a single IRB.

Providing the resources to train, cultivate, and sustain future leaders of the biomedical research workforce is another key CTSA Program emphasis. The program supports a coordinated, national effort to help ensure a pipeline of trained translational investigators who

can move basic research findings into applications for improving health outcomes as novel therapies, diagnostics, and preventives. Program grantees have developed clinical and translational sciences training resources, including educational core competencies, best practices for training mentors, and curriculum materials. These tools are freely available, and many institutions nationwide are using them.

Engaging patients at all stages of translation is crucial; their perspectives as members of the research team provide insights, focus, urgency and connectivity that can be instrumental in making the development, testing and deployment of new interventions more effective. NCATS supports the Rare Diseases Clinical Research Network (RDCRN) and requires each consortia member to include patient groups as full partners on their research teams, an approach that helps achieve greater success. The RDCRN Coalition of Patient Advocacy Groups develops and shares best practices, and the RDCRN website includes a contact registry for patients who may be interested in participating in RDCRN clinical studies. Rare diseases, which cumulatively affect approximately one in 10 people in the U.S., are in crucial need of innovative translational technologies, and are thus a crucial NCATS focus.

Measurable outcomes can help determine whether a new translational process is actually an improvement. NCATS' Discovering New Therapeutic Uses for Existing Molecules program matches academic investigators with pharmaceutical companies that have compounds that were found to be ineffective in treating specific diseases. Repurposing these compounds for potentially treating other diseases saves time in the drug development process because significant foundational work already has been completed. NCATS helps to further accelerate this process by providing collaboration agreement templates that now are being used broadly in the research community and by supporting researchers with new ideas for how existing compounds can be repurposed.

Finding New Therapies for Clinical Study

NCATS also is dedicated to removing pre-clinical translational science roadblocks. Through its Therapeutics for Rare and Neglected Diseases (TRND) program, the Center works to “de-risk” potential therapeutics so that private sector companies may be more inclined to acquire them to finish their development.

Despite promising results in clinical trials outside of the U.S., work on further developing a gene therapy for the rare pediatric disease aromatic L-amino acid decarboxylase (AADC) deficiency was seemingly insurmountable. Through TRND, NCATS teamed with a private sector partner, Agilis Biotherapeutics, to convert promise into reality, jointly creating a manufacturing process for a therapy that complies with FDA regulations, and obtaining the required pre-clinical data. In addition to getting this potentially lifesaving therapy to patients, this project established technological and regulatory models that will accelerate development of other rare disease gene therapies.

The NCATS Cures Acceleration Network (CAN) supports high-risk, innovative programs to advance the development of high-need cures and reduce significant barriers between research discovery and clinical trials. Through the CAN-funded Tissue Chip for Drug Screening

program, NCATS is working on new methods for predicting both safety and efficacy of experimental drugs using engineered “chips” that contain human cells and model human organs. Current methods such as animal and cell models are not always reliably predictive and can result in wasted time and effort. In addition to developing these chips for testing potential drugs, NCATS soon will send tissue chips to the International Space Station (ISS) for research on the effect of microgravity on these model organs. Microgravity can accelerate aging and have other effects relevant to diseases on Earth, making the ISS a unique and significant research environment.

New drug development for currently untreatable diseases has been greatly limited because known chemical structures affect only 10 percent of potential drug targets within the human body. With CAN support, NCATS plans to launch its Automated Synthesis Platform for Innovative Research and Execution (ASPIRE) program to bring together chemistry, robotic engineering, biological activity testing, and artificial intelligence. Tools developed through ASPIRE will minimize the time chemists spend on tedious and repetitive tasks, freeing them up for more complicated pursuits such as designing, synthesizing, and testing compounds for diseases that currently have no treatment.

Adaptability to Tackle Emerging Public Health Needs

With its unique collection of programs, initiatives and resources, NCATS has the capacity and capability to address public health crises. For example, a team of researchers from NCATS and the Icahn School of Medicine at Mount Sinai developed a miniaturized assay for high-throughput screening to find compounds that block the ability of Ebola virus-like particles (VLPs) to enter and infect cells. A screen using 2,816 compounds identified 53 drugs with entry-blocking activity against Ebola VLPs.

In another example, investigators from Johns Hopkins University and Florida State University collaborated with NCATS experts on drug repurposing and high throughput screening to identify rapidly two classes of existing compounds that potentially can be used to fight Zika. These compounds were effective either in inhibiting the replication of the Zika virus or in preventing the virus from killing brain cells. All data have been made available through public databases, allowing these compounds to be further studied by the broader research community.

NCATS also is well-positioned to help combat the current national epidemic of opioid abuse. The Center’s high-throughput screening facility could be used to test potential opioid abuse therapeutics, and CTSA Program-supported researchers could help identify opioid patients and rapidly enroll them in multisite clinical trials.

Conclusion

Through its programs and initiatives described above, and others, NCATS is improving health through smarter science in unprecedented ways, with the ultimate goal of getting more treatments to more patients — and to the public at large — more quickly.

Christopher P. Austin, M.D.
Director, National Center for Advancing Translational Sciences

Dr. Austin leads NCATS' work to improve the translation of observations in the laboratory, clinic and community into interventions that reach and benefit patients—from diagnostics and therapeutics to medical procedures and behavioral changes. Under his direction, NCATS researchers and collaborators are developing new technologies, resources and collaborative research models; demonstrating their usefulness; and disseminating the data, analysis and methodologies for use by the worldwide research community.

Dr. Austin's career has spanned the spectrum of translational research, in the public and private sectors. Dr. Austin joined NIH in 2002 as the senior advisor to the director for translational research at the National Human Genome Research Institute, where he was responsible for conceptualizing and implementing research programs to derive scientific insights and therapeutic benefit from the newly completed Human Genome Project. While at NHGRI, he founded and directed the NIH Chemical Genomics Center, Therapeutics for Rare and Neglected Diseases program, Toxicology in the 21st Century initiative, and NIH Center for Translational Therapeutics. Upon the creation of NCATS in 2011, he became the inaugural director of the NCATS Division of Pre-Clinical Innovation and was appointed NCATS director in 2012. In 2016, Dr. Austin was elected chair of the International Rare Disease Research Consortium (IRDiRC). Prior to joining NIH, Dr. Austin worked at the pharmaceutical company Merck, where he directed programs on genome-based discovery of novel targets and drugs, with a particular focus on schizophrenia and Alzheimer's disease.

Dr. Austin is trained as a clinician and geneticist. He trained in internal medicine and neurology at the Massachusetts General Hospital in Boston and practiced medicine in academic and community hospital settings as well as in urban primary care and in rural Alaska and Africa. He completed a research fellowship in developmental neurogenetics at Harvard, studying genetic and environmental influences on stem cell fate determination. Dr. Austin earned an M.D. from Harvard Medical School and A.B. *summa cum laude* in biology from Princeton University.

**PREPARED STATEMENT OF DAVID SHURTLEFF, PH.D.
ACTING DIRECTOR, NATIONAL CENTER FOR COMPLEMENTARY AND
INTEGRATIVE HEALTH**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Center for Complementary and Integrative Health (NCCIH) of the National Institutes of Health (NIH).

The mission of NCCIH is to define, through rigorous scientific investigation, the safety and effectiveness of complementary and integrative health approaches, which are a group of practices and products that originate outside of conventional medicine. This diverse group of health practices includes natural products such as dietary supplements, plant-based products, and probiotics, as well as mind-body approaches such as yoga, massage therapy, meditation, mindfulness-based stress reduction, spinal manipulation, and acupuncture. According to a 2012 National Health Interview Survey (NHIS), Americans are spending approximately \$30.2 billion a year on complementary approaches to improve their overall health, manage symptoms of chronic diseases, and/or counter the side effects of conventional medicine. However, the scientific research base surrounding the safety and efficacy of these practices is limited. Therefore, NCCIH is committed to providing the American public with valuable information about these practices, while also investigating how specific complementary approaches can be integrated into conventional medical care.

EXPLORING NONPHARMACOLOGIC APPROACHES FOR PAIN MANAGEMENT

NCCIH is devoting significant resources to understand the basis of pain and how complementary and integrative health approaches can be utilized in pain management. Pain is a major public health problem and is the most common reason Americans turn to complementary and integrative health practices. Data from the 2012 NHIS found that an estimated 25.3 million adults in the U.S. (11.2 percent) experience daily pain with nearly 40 million adults (17.6 percent) experiencing severe levels of pain. The use of highly addictive opioids as a primary pain management strategy in the U.S. is helping to fuel the growing opioid misuse epidemic. Improved strategies for pain management may lead to a decreased reliance on opioids for patients suffering from pain. NCCIH supports research to better understand the biologic mechanisms of pain and to identify effective nonpharmacologic approaches to reduce the duration and intensity of pain.

Research supported at NCCIH is focused on understanding the role of the brain in perceiving, modifying, and managing pain, with the long-term goal of improving clinical management of chronic pain through the integration of pharmacologic and nonpharmacologic approaches. Recently, scientists discovered a new class of sensory nerve cells that respond to high-threshold (intense) mechanical stimuli, such as hair pulling. This work provides insights into how our bodies encode and transmit pain sensations. Another study mapped the regions of the brain activated during pain to establish a "pain signature" and found that specific regions of the brain respond to pain intensity, while other regions mediate the psychological effect, and yet another region showed increased activity related to pain relief. This work not only provides

insights into how pain is interpreted but could lead to the development of new methods to detect, quantify, or target pain.

NCCIH-supported research is also advancing understanding of the mechanisms of action of mind and body interventions and determining their effectiveness for treating pain. One study investigated the effect of acupuncture on carpal tunnel syndrome and found that it affected activity within brain pain centers, decreased associated pain symptoms, and improved overall wrist function. Mindfulness meditation is another promising area of research. Numerous studies have shown that mindfulness meditation helps relieve pain, but the mechanism through which meditation exerts this effect is not well known. New study results demonstrate that mindfulness meditation activates the same region of the brain as opioids; however, it reduces pain independently of opioid neurotransmitter mechanisms. These results suggest that greater pain control could be achieved through the combination of mindfulness meditation and opioid-signaling-induced pharmacologic approaches. NCCIH-supported research has also shown that mindfulness-based stress reduction and cognitive behavioral therapy can improve functioning and reduce chronic low back pain in young and middle-aged adults and may provide patients with skills for long-term management of pain. Studies have demonstrated that these approaches resulted in substantial cost savings over usual care.

Based on these and other promising results, NCCIH is leading a new multi-agency partnership between the NIH, Department of Defense (DoD) and Department of Veterans Affairs (VA). This initiative, called the NIH-DoD-VA Pain Management Collaboratory (PMC), addresses the need to focus on “advancing better practices for pain management,” which is outlined in HHS’s five-point strategy to combat the opioid crisis. The PMC will focus on developing, implementing, and testing cost-effective, large-scale, real-world research on nondrug approaches for pain management and related conditions in military and veteran health care delivery organizations. The PMC launched in FY2017 and the agencies plan to fund 11 two-year UG3 (Planning Phase) awards, and up to 10 four-year subsequent UH3 (Implementation Phase) Demonstration Projects, contingent upon successful completion of the short-term pilot and feasibility studies. In addition, a PMC Coordinating Center has been established at Yale University and the Veteran’s Administration Hospital in Connecticut to provide leadership and serve as a resource for the projects by providing innovative tools and best practices. Types of approaches being studied include mindfulness/meditative interventions, movement interventions (e.g., structured exercise, tai chi, yoga), manual therapies (e.g., spinal manipulation, massage, acupuncture), psychological and behavioral interventions (e.g., cognitive behavioral therapy), integrative approaches that involve more than one intervention, and integrated models of multi-modal care. The results of these studies may inform new pain management practices within the DoD and VA and support the use of nondrug approaches for pain management in the general population.

ADVANCING RESEARCH ON NATURAL PRODUCTS

According to the 2012 NHIS, nearly one in five U.S. adults use botanical supplements and other non-vitamin, non-mineral dietary supplements, such as fish oil/omega-3 fatty acids and probiotics. Adverse events related to dietary supplements are estimated to contribute to 23,000 emergency department visits in the U.S. each year. To better inform consumers and their health

care providers, NCCIH supports rigorous research on the biological mechanisms of the benefits and potential harmful effects of natural products with the goal of improving the body of knowledge available to health care providers and patients.

NCCIH is supporting a Center of Excellence to determine how best to study potential adverse interactions between natural products and conventional medications. The goal is to develop a definitive approach to determine the clinical relevance of supplement-drug interactions to inform design of future research and, ultimately, decision-making about using natural products and medications together.

In FY2015, NCCIH partnered with NIH's Office of Dietary Supplements (ODS) to establish the Centers for Advancing Research on Botanical and Other Natural Products (CARBON) Program. Through this program, researchers recently identified two chemicals found in grapes that could significantly reduce depression-like behaviors in mice. The systems targeted by these compounds are not the same as current pharmaceutical antidepressants and may provide novel insights into the biology of depression and could lead to new therapeutic agents. The program is also developing new methods for chemical characterization of natural product mixtures, biological profiling assays, and creating new informatic tools to rigorously analyze and share data.

NCCIH is also supporting research on cytosine, a natural product for smoking cessation. Despite promising results from clinical trials conducted outside the U.S., cytosine has not yet been approved for use in the U.S. NCCIH supported a series of pre-clinical studies on cytosine through a strategic collaboration with Achieve Life Sciences, Inc., OncoGenex Pharmaceutical, Inc., other NIH ICs, and private research organizations. Phase 2 clinical studies will further assess cytosine as a smoking cessation treatment. This continuing public-private partnership may lead to the wide availability of a new option to address the major public health issues associated with tobacco use.

CONCLUSION

As a responsible steward of resources, NCCIH supports scientifically meritorious basic, mechanistic, clinical, and translational research. The Center focuses on areas with the greatest potential impact by prioritizing research topics that show scientific promise and are amenable to rigorous scientific inquiry. We leverage strategic partnerships to build the scientific evidence needed on the safety and efficacy of complementary health approaches and disseminate evidence-based information to the American public.

David Shurtleff, Ph.D.

Acting Director, National Center for Complementary and Integrative Health

David Shurtleff, Ph.D., is Acting Director of the National Center for Complementary and Integrative Health (NCCIH), performing a wide range of activities aimed toward directing and implementing a program of research that builds a scientific evidence base about complementary and integrative health approaches that advances fundamental knowledge, and informs decision making by the public, health care professionals, and health policymakers. Dr. Shurtleff's 23-year career at the National Institutes of Health (NIH) has focused on providing leadership and fostering an extensive research portfolio in the basic behavioral and neurosciences—cognitive studies, behavioral economics, decision theory, and risk-taking—and a broad spectrum of research that has contributed to cutting-edge research related to drug abuse, addiction, and their treatment.

Prior to becoming Acting Director, NCCIH, Dr. Shurtleff served as the Deputy Director of NCCIH. Prior to joining NCCIH he served as the Acting Deputy Director of the National Institute on Drug Abuse (NIDA). At NIDA, he helped develop, implement, and manage the Institute's broad grant portfolio covering basic cellular, molecular, and systems neurobiology as well as behavior, treatment, medication development, clinical neuroscience, clinical trials, prevention, and health services research. Prior to joining NIDA, Dr. Shurtleff was a research psychologist at the Naval Medical Research Institute in Bethesda, Maryland, where he conducted basic behavioral, electrophysiological, cognitive, and field research on a variety of issues related to cognitive performance, environmental stress, and peripheral neuropathy. He also served as a research fellow at the Walter Reed Army Institute of Research in the Department of Medical Neurosciences. Dr. Shurtleff holds a B.S. degree from the University of Massachusetts. He received his M.A. and Ph.D. degrees in experimental psychology from American University. He has received various honors and awards including several NIH Director's Awards. One of these awards recognized his outstanding contributions to the 2014 President's BRAIN Initiative.

**PREPARED STATEMENT OF NORMAN E. SHARPLESS, M.D.
DIRECTOR, NATIONAL CANCER INSTITUTE**

Mr. Chairman and Members of the Committee, I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH). With the resources that this subcommittee provides, NCI supports a broad array of biomedical research to advance scientific discovery, reduce the burden of cancer, and help all people live longer, healthier lives.

NCI Progress under the 21st Century Cures Act

In the Cures Act, Congress authorized \$1.8 billion across seven fiscal years for the Cancer Moonshot. The FY 2018 Consolidated Appropriations Act provided the second Cures Act installment of \$300 million. Guided by the recommendations of a Blue Ribbon Panel convened to identify research priorities, NCI awarded FY 2017 funding in ten promising areas of cancer research targeted for rapid translation into new treatment and prevention. NCI will fund all remaining Blue Ribbon priorities during FY 2018.

One example of NCI's commitment to the progress envisioned in the Cures Act is the promising area of immunotherapy – activating a patient's immune system to attack cancer cells. To accelerate the development of immunotherapy strategies for cancer patients, in the fall of 2017, NCI launched a public-private partnership with NIH and pharmaceutical companies, known as the Partnership for Accelerating Cancer Therapies, or PACT. The Foundation for the National Institutes of Health will manage and coordinate PACT, and the Food and Drug Administration will play an essential advisory role. Twelve pharmaceutical companies are now members of PACT.

A centerpiece of PACT is NCI's \$54 million investment of Cures Act funds across five fiscal years to establish four Cancer Immune Monitoring and Analysis Centers and a Cancer Immunologic Data Commons. Together, the centers and data commons will operate as a network to identify mechanisms of response and resistance to cancer therapy and to support adult and pediatric immunotherapy trials.

NCI created the immunotherapy network to speed discovery of molecular signatures associated with immune response and to predict whether immunotherapy will benefit individual patients. The network will identify biological markers of disease and response to treatment that researchers and clinicians can use to design optimum treatment strategies for cancer patients. The entire cancer research community can access data from analysis conducted by the four centers and use this resource to further their research on cancer cures. Other priorities of the NCI immunotherapy network and the 12 PACT partners include establishing a set of standardized biomarkers for testing in research studies, harmonizing assays to strengthen data reproducibility, fostering data comparability across clinical trials, and reducing duplication of effort, thereby allowing researchers to conduct more high-quality clinical trials for children and adults with cancer.

In addition to support for PACT, NCI also awarded Cures Act funding to other promising research on harnessing the immune system to attack cancer. The goal of this research is to expand the initial successes in immunotherapy to a much wider range of cancers, to a broader range of patients experiencing the same form of cancer, and to cancers that have been most resistant to cure.

Appropriations for Other Cancer Research Priorities

While the 21st Century Cures Act deserves prominence in any discussion of NCI's current cancer research priorities, as a component of our total budget, FY 2017 Cures Act funding represented about five percent of NCI's total cancer research appropriation. It is therefore important to emphasize the breadth of other research that NCI's appropriation conducts.

As the detailed narrative accompanying NCI's budget request demonstrates, sustained progress that will benefit cancer patients relies on many forms of research, including:

- basic research, such as genetics, cell biology, immunology, and structural biology
- translational and clinical sciences to prevent, screen, and diagnose cancer, and to develop and test drugs, biomarkers, imaging technologies, diagnostics, and radiotherapies
- population sciences, including epidemiological, environmental, and behavioral studies.

These areas constitute the bedrock of NCI cancer research. Continued funding across all these disciplines is essential to understanding the causes and mechanisms of cancer, preventing cancer, strengthening cancer screening, developing and refining cancer therapies, and improving cancer survivorship. Many of these disciplines will experience profound changes based on the new understanding of cancer that is driving precision oncology and to tailor treatments to individuals. Others will continue to depend on more traditional approaches to research.

The research resources that NCI makes available to the cancer research community is another mechanism of growing importance to cancer science. Examples of NCI research resources include:

- The Biopharmaceutical Development Program (BDP) produces novel antibodies and proteins when they cannot be manufactured elsewhere. For example, researchers turned to the BDP to manufacture a monoclonal antibody (ch14.18) necessary for a clinical trial to proceed. The antibody is now the standard of care for children with certain types of neuroblastoma.

During FY 2018, NCI will use the capability of the BDP to expand production of CAR T-cells for use in immunotherapy trials. The BDP will help meet the growing demand for experimental therapies to serve adult and pediatric patients in intramural and extramural clinical trials. CAR T-cell therapy is an immunotherapy treatment in which a patient's T-cells (a type of immune cell) are modified in the laboratory so they bind to cancer cells. Millions of CAR T-cells are grown in the laboratory and then given to the patient by infusion, where they bind to an antigen on cancer cells and kill them.

- NCI's Experimental Therapeutics (NExT) program advances breakthroughs in new cancer therapies by shortening the timeline for drug discovery, development, and approval. Researchers with promising cancer drug development projects can apply to NExT for assistance to overcome the challenges they face along the path to drug approval.

Vanderbilt University's recent progress developing therapies to inhibit a protein known as Mcl-1 is an example of the breakthroughs that NExT helps to foster. After engaging NExT scientists to resolve therapeutic development challenges, Vanderbilt is now collaborating with Boehringer Ingelheim to develop drugs to treat a range of cancers known to overexpress the Mcl-1 protein.

- NCI's RAS Initiative supports the development of therapies for tumors that contain mutations in the RAS family of oncogenes. One-third of all cancers involve RAS gene mutations. Through the RAS Initiative, NCI generates standardized reagents, assays, and datasets and provides them to scientists worldwide to support research on RAS oncogenes.
- The Cancer Genome Atlas (TCGA) – a collaboration between NCI and the National Human Genome Research Institute – is a resource of comprehensive, multi-dimensional maps of key genomic changes in 33 types of cancer. The publicly-available TCGA dataset – containing 2.5 petabytes of data – has contributed to more than a thousand cancer studies. An NCI priority for FY 2018 is to update TCGA data with new details on patient therapeutic response, outcome, and survival, and to support additional clinical research based on the new data.
- Launched in June of 2016, NCI's Genomic Data Commons (GDC) is a unified data system for sharing genomic and clinical data. The GDC centralizes and standardizes data from large-scale NCI programs, and makes it more accessible and useful to scientists and clinicians. One measure of the importance of this resource is that non-profit and for-profit organizations are now offering their data sets for sharing through the GDC.

I also want to highlight our progress with the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) Trial and the Pediatric MATCH Trial, two cornerstones of NCI's Precision Medicine Initiative. Rather than selecting therapies based on where a tumor originated in the body, these trials test the effectiveness of therapies that target specific genetic changes. In 2017, the adult NCI-MATCH Trial achieved its enrollment goal nearly two years ahead of schedule. The trial involves more than 6,000 patients from all 50 states at more than 1,000 institutions.

NCI opened enrollment for the Pediatric MATCH Trial during FY 2017. This is a phase 2 clinical trial for children and adolescents with certain advanced solid tumors that have not responded to treatment or have progressed on standard therapy. The study is led jointly by NCI and the Children's Oncology Group, a clinical trials group including more than 9,000 childhood cancer experts across 3 continents that is part of the NCI-sponsored National Clinical Trials Network. The Pediatric MATCH trial is taking place at 200 participating children's hospitals, university medical centers, and cancer centers across the United States.

Thanks to support from Congress over many years, NCI research in these and other areas has yielded important results that have contributed to steady decreases in cancer mortality. Sustained Congressional support for NCI and the national cancer program has led to new diagnostics, treatments, and prevention strategies, improved our ability to manage the symptoms of cancer and the side effects of cancer treatments, and allowed us to more effectively monitor the prevalence of cancers and the factors associated with cancer risk.

NCI-led cancer research on prevention and treatment is paying off: translating into a more than 25 percent reduction in cancer death rates since 1991. Yet despite steady progress, too many Americans face a cancer diagnosis, and far too many still die from the disease. There will be more than 1.6 million new cases of cancer in the United States in the coming year and more than 600,000 will likely die from cancer.

Thus, much work remains to meet the needs of those suffering from cancer, those at risk of cancer, and the growing population of cancer survivors. The resources proposed in this FY 2019 budget will allow NCI to continue to conduct our cancer research mission in ways that deliver important results for the patients we serve.

Dr. Norman E. Sharpless
Director, National Cancer Institute

Norman E. “Ned” Sharpless, M.D., was officially sworn in as the 15th director of the National Cancer Institute (NCI) on October 17, 2017. Prior to his appointment, Dr. Sharpless served as the director of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center, a position he held since January 2014.

Dr. Sharpless was a Morehead Scholar at UNC–Chapel Hill and received his undergraduate degree in mathematics. He went on to pursue his medical degree from the UNC School of Medicine, graduating with honors and distinction in 1993. He then completed his internal medicine residency at the Massachusetts General Hospital and a hematology/oncology fellowship at Dana-Farber/Partners Cancer Care, both of Harvard Medical School in Boston.

After 2 years on the faculty at Harvard Medical School, he joined the faculty of the UNC School of Medicine in the Departments of Medicine and Genetics in 2002. He became the Wellcome Professor of Cancer Research at UNC in 2012.

Dr. Sharpless is a member of the Association of American Physicians as well as the American Society for Clinical Investigation (ASCI), the nation’s oldest honor society for physician–scientists, and served on the ASCI council from 2011 to 2014. Dr. Sharpless was an associate editor of *Aging Cell* and deputy editor of the *Journal of Clinical Investigation*. He has authored more than 150 original scientific papers, reviews, and book chapters, and is an inventor on 10 patents. He cofounded two clinical-stage biotechnology companies: G1 Therapeutics and HealthSpan Diagnostics.

In addition to serving as director of NCI, Dr. Sharpless continues his research in understanding the biology of the aging process that promotes the conversion of normal self-renewing cells into dysfunctional cancer cells. Dr. Sharpless has made seminal contributions to the understanding of the relationship between aging and cancer, and preclinical development of novel therapeutics for melanoma, lung cancer, and breast cancer.

PREPARED STATEMENT OF DR. PAUL SIEVING DIRECTOR, NATIONAL EYE INSTITUTE

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year 2019 budget request for the National Eye Institute (NEI) of the National Institutes of Health.

FIFTY YEARS OF VISION RESEARCH

It may have been a hot day on August 16, 1968, when President Johnson signed Public Law 489 to create the National Eye Institute, but on March 21, 2018, the biggest blizzard of the season threatened a reception hosted by Congressman Pete Sessions to celebrate NEI's 50th anniversary. However, snow didn't deter over 100 vision research stakeholders, National Institutes of Health scientists, patients, and members of Congress from coming out to recognize the vision-saving progress made in the past half century. While my statement usually covers the latest advances, I want to start by reflecting on some of our remarkable research progress, which has advanced clinical vision care.

Over the past 50 years, NEI has funded research of nine Nobel Prize winning scientists, including discovery of the molecular mechanisms by which specialized neurons in the retina detect photons of light entering the eye and initiate biochemical and electrical signals to the brain that convey vision. The key light-detecting protein, rhodopsin, became the first cell membrane-bound protein studied by x-ray crystallography and imaged to reveal the protein structure in three dimensions. This paved the way for the study of other molecules in diseases in and beyond the eye. NEI-funded Nobel laureates also made landmark neuroscience discoveries of how brain circuits form and self-organize in the visual cortex. This has revolutionized treatment for amblyopia, a disorder in which the brain favors visual information coming from one eye over the other. The first use of antiviral chemotherapy was developed for the eye to treat herpes outbreaks on the cornea. In ground-breaking work, NEI scientists discovered the first tumor suppressor gene, *retinoblastoma*, which transformed all of cancer biology. Conversely, in the past decade, the ocular adaptation of a cancer drug that blocks growth of abnormal blood vessels treats two of the leading causes of blindness: age-related macular degeneration (AMD) and diabetic retinopathy, stopping disease progression, and in many cases, reversing vision loss for medical benefit to thousands of patients.

In its early years, NEI pioneered new methodology for conducting placebo-controlled, multi-center clinical trials, which led to vision-saving laser surgery to treat diabetic retinopathy, AMD, and glaucoma. Large trials identified dietary supplements demonstrated to slow progression to end-stage AMD. Trials compared effectiveness of different therapies for AMD, diabetic retinopathy, and an inflammatory eye condition called uveitis, to inform patients and their doctors of options for personalized treatment. Elevated fluid pressure in the eye, called ocular hypertension, is a precursor for glaucoma, especially in African Americans who have a disproportionate burden of this disease. 1,500 patients participated in the Ocular Hypertension Treatment Study, including 400 African American participants, which led to new treatment guidelines that can reduce incidence in African Americans by 50 percent. A 20-year follow-up

study is currently underway to assess the long-term impact. More recently, the first application of genomics methods led NEI scientists to uncover new genetic components for AMD, opening the door to new treatments. Before NEI was established, a major cause of lifelong blindness was retinopathy-of-prematurity (ROP), a disease caused by abnormal development of retinal blood vessels in low birth weight babies born very prematurely. Technology to identify and treat ROP has improved dramatically over the years and a recent NEI trial demonstrated that premature infants can be screened for ROP remotely via telemedicine, expanding access to specialists in rural and underserved communities.

RECENT PROGRESS IN VISION RESEARCH

NEI-supported vision research remains on the forefront of medicine, from regenerative medicine to replace neural tissue lost due to retinal degeneration; to advancing retinal prosthetics, including the Argus II artificial retina which was approved by FDA through the Humanitarian Device Exemption pathway; and pioneering the application of gene therapy to correct blinding disease-causing mutations. One landmark occurred in December 2017, when the FDA approved the first ever gene therapy in the U.S. to correct a retinal degeneration, Leber Congenital Amaurosis, which causes blindness in infants and children. The genetic mutation had earlier been discovered by an NEI scientist in 1993, but researchers had to invent the tools to turn that discovery into a gene therapy. Having set this precedence for all of medicine, the path from gene discovery to clinical trial is now being expedited with vision loss mutations in a dozen genes currently being addressed in pre-clinical and clinical studies.

Also in December, FDA approved two new drugs for glaucoma, the first new medications for this disorder in 18 years. This new class of drugs lowers pressure in the eye through novel targets that are different from existing medications. An ongoing clinical trial is testing a combination therapy of the newer and older drugs used together, which may prove more effective than either drug alone. This research represents the culmination of over 25 years of NEI basic research on molecules that control the contractile machinery of cells, which regulate the flow of fluid out of the eye.

Idiopathic intracranial hypertension (IIH), which primarily affects obese young women, causes the buildup of pressure on the optic nerve, leading to vision loss in nearly 10 percent of patients. The recently completed IIH Treatment Trial of 165 patients showed that for mild vision loss, intervention with acetazolamide plus diet was superior to diet alone for reducing vision loss and improving quality of life. However, neither intervention was effective for patients with moderate to severe vision loss. NEI is funding a new three-arm trial testing different surgical interventions to relieve pressure and protect the optic nerve in 180 IIH patients with more severe vision loss.

SEEING INTO THE FUTURE

The NEI Audacious Goals Initiative (AGI) seeks to restore vision through neuroregeneration in the eye and visual system. This fundamental regenerative medicine approach was initiated in 2013 and is advancing rapidly. NEI has established two collaborative consortia of research teams working on different facets of the challenge: one on functional

imaging, and a second for discovery science to identify new regeneration factors by looking in model systems. For example, unlike adult mammals, zebrafish can regenerate their retina after injury, which led NEI researchers to identify a key regeneration factor, present in newborn mice, and through manipulating this factor, they caused new neurons to form in adult mice. Scientists also found that exosomes secreted from stem cells protect a type of retinal cells, the ganglion cells, which are damaged by glaucoma. Exosomes are now being examined for potential therapeutic effect. Exosome-treated rats lost only a third of their retinal ganglion cells following optic nerve injury, compared with 90 percent loss in untreated rats. NEI is now reviewing proposals for a third AGI consortium, to develop animal model systems to facilitate translation of discovery research into the clinic.

NEI just launched new stem cell trials for retinal vein occlusion (RVO)—the second leading retinal vascular cause of vision loss after diabetic retinopathy, and for limbal stem cell deficiency (LSCD). In RVO, the vessels draining blood from retinal tissue become clotted, leading to leaking and bleeding and ultimately starving the neurons of oxygen. The trial will test the safety, feasibility and efficacy of injecting stem cells derived from the patient’s own bone marrow into their eyes. Corneal limbal cells, are responsible for renewing the front layer of the transparent cornea. In thousands of patients with LSCD, loss of these cells causes visual impairment from chronic inflammation, abnormal blood vessel growth, and opaque corneas. The 21st Century Cures Act Regenerative Medicine Program is supporting an NEI project to treat LSCD. Researchers identified a limbal cell marker, ABCB5, which has allowed them to isolate, purify and expand limbal stem cells in the lab in sufficient quantities for transplantation. This summer, NEI scientists are about to launch the first clinical trial using induced pluripotent stem cells-derived retinal tissue to treat the dry form of AMD. Skin cells taken from AMD patients will be manipulated in the lab for about three months, then transplanted back into the same patients, thereby minimizing rejection of foreign tissue that affects many types of transplant therapies.

In 2017, NEI launched a 3D Retina Organoid Challenge Competition (3D-ROC), with the goal of developing functioning “mini-retinas” in a culture dish from human adult stem cells. In September, NEI awarded the \$90,000 prize for the Phase I Ideation Stage, to a team that developed the concept of building a retina by screen-printing adult neural progenitor-derived retinal cells in layers that mimic the structure of the human retina. The system is designed to be scalable, efficient, and reproducible, enabling high throughput screening for drug testing. In February 2018, NEI launched Phase II, which soon will award up to \$1 million in prizes for developing this work to the critical stage of functional prototypes of human retinas.

In January, NEI announced the launch of a new strategic planning process, under the auspices of the National Eye Advisory Council. The five-year plan will be developed with significant community input, centered around scientific program working groups. It will also align with the NIH Strategic Plan and requirements laid out in the 21st Century Cures Act, including research to address health disparities.

Paul Sieving, M.D., Ph.D.
Director, National Eye Institute

Dr. Sieving is Director of the National Eye Institute, NIH. Previously he was the Paul R. Lichter Professor of Ophthalmic Genetics at the University of Michigan (1985-2001). Dr. Sieving studied nuclear physics at Yale Graduate School (1970-73) and attended Yale Law School (1973-74). He received his MD (1978) and PhD (bioengineering, 1981) degrees from the University of Illinois. After an ophthalmology residency at the University of Illinois Eye and Ear Infirmary under Mort Goldberg (1982-85), he did post-doctoral work in retinal physiology with Roy H. Steinberg at the University of California San Francisco (1982-83) and a clinical fellowship in retinal degenerations with Eliot Berson at Harvard Medical School, Massachusetts Eye and Ear Infirmary (1984-85).

Dr. Sieving is known internationally for clinical and basic studies of genetic retinal neurodegenerations, including retinitis pigmentosa and macular degeneration. As a clinician, he provides ophthalmic care to patients and their families with Mendelian traits that cause photoreceptor dysfunction and neurodegeneration. He is also a tenured Senior Investigator in the NIH Intramural Research Program. His laboratory focuses on the pathophysiology of photoreceptor disease and synapses to the other retinal neurons as well as glial interactions. His studies of pharmacological approaches to slow degeneration in retinal transgenic animal models led to the first human clinical trial of ciliary neurotrophic factor (CNTF) for retinitis pigmentosa, published in *PNAS*, 2006. He developed a mouse model of X-linked retinoschisis (XLRs) and treated this successfully using gene therapy which restored retinal function. He initiated the first human XLRs gene therapy trial at NIH in 2015 for XLRs (ClinicalTrials.gov # NCT02317887).

Dr. Sieving is an elected member of both the National Academy of Medicine of the National Academies and the German National Academy of Sciences. He previously served as Vice Chair for Clinical Research for the Foundation Fighting Blindness from 1996-2001. He is an award jury member for the €1 million annual 'Vision Award' of the Champalimaud Foundation, Portugal. He was elected to membership in the American Ophthalmological Society in 1993 and the Academia Ophthalmologica Internationalis in 2005. He has received many honorary awards including the Research to Prevent Blindness Senior Scientific Investigator Award; the Alcon Research Institute Award; Pisart Vision Award from the New York Lighthouse International for the Blind and most recently, the Pyron Award, which was created by the Retina Research Foundation of Houston to recognize outstanding vision scientists whose work contributes to knowledge about vitreoretinal disease.

**PREPARED STATEMENT OF ERIC D. GREEN, M.D., PH.D.
DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH).

The Forefront of Genomics

NHGRI is, and always has been, at the forefront of genomics research. NHGRI led the U.S. contribution to the Human Genome Project, which was completed in 2003, and has since embarked on evermore ambitious endeavors, including the dissemination of genomic technologies, knowledge, and expertise throughout the NIH, into the private sector, and around the world. NHGRI accomplished this by driving cutting-edge research, developing new methods and approaches, and studying the impact of genomics on society with the goal of improving the health of all humans through genomic advances. The current pace of genomics is breathtaking, and we are approaching a transitional time in which there will be rapid uptake of genomics in medicine for prevention, diagnosis, and treatment of disease.

To prepare to lead the next phase of genomics, NHGRI officially launched a new strategic planning process in early 2018. This 2-year effort will generate a '2020 Vision for Genomics' and position the Institute to lead genomics research and its applications to human health into the next decade.

Our strong tradition of audacious thinking and effective strategic planning has led to advances that today are enabling some of the most high-profile initiatives in biomedical research. Examples include the NIH *All of Us* Research Program, which seeks to build the largest, most diverse dataset of its kind for health researchers, and the Cancer Moonshot initiative, which aims to accelerate cancer research and to improve our ability to detect, prevent, and treat cancer. The NHGRI-funded Electronic Medical Records and Genomics (eMERGE) Network, now in its third phase, has served as an invaluable pilot for precision medicine research studies, like *All of Us*, by developing the tools and approaches for using genomic information coupled with data in electronic medical records to study human health and disease, including prevention. The Cancer Genome Atlas (TCGA), equally funded by NHGRI and the National Cancer Institute (NCI), generated comprehensive maps of key genomic changes in 33 types of cancer and made all the generated data publicly available to the research community; this program provided a foundation upon which the molecular bases of cancer continue to be defined, revealing new approaches for cancer treatments. In addition, efforts like TCGA and the Cancer Moonshot heavily rely on the dropping costs of genome sequencing, which has been greatly facilitated by NHGRI's technology development research programs.

As noted earlier, the uptake of genomic medicine approaches will increase rapidly in the coming years, and NHGRI is committed to laying the groundwork for these changes. An example effort that will be underway in FY 2019, if funding allows, is the Clinical Sequencing Evidence-Generating Research Program (CSER), which aims to generate and analyze evidence for the use

of genome sequencing in clinical care and to address barriers to genomic medicine implementation. This program has a targeted focus on recruiting ancestrally diverse and underserved populations, recognizing that the full benefit of genomic medicine will not be realized unless all of the diverse populations in the United States benefit equitably from genomic advances.

Compared to even a decade ago, genomics is now associated with a much greater breadth and depth of research activities. Furthermore, influenced by NHGRI's leadership, virtually every NIH Institute and Center now funds genomics research to some extent, and a significant amount of genomics research is funded beyond NIH. Recognizing that going forward, a majority of genomics research will be funded by others in the U.S. and internationally, NHGRI aims to identify, lead, and support areas of genomics that are paradigm-setting, that enable novel applications, and that expand the field – all with a focus on applications to human health and disease. In doing so, NHGRI will directly stimulate and achieve highly impactful and generalizable progress in genomics that will benefit the efforts of others for years to come.

Research

Our foundational work in technology development, coupled with new approaches for elucidating genome function, is fueling discoveries of how genomic variation relates to human health and disease; in turn, this knowledge is increasingly being applied to patient care through pilot projects that study the implementation of genomic medicine.

In FY 2019, if funding allows, NHGRI's longstanding Genome Sequencing Program will continue its fundamental work to identify genomic variants associated with disease and to provide resources for the research and clinical communities to discover the genomic underpinnings of disease. The Centers for Common Disease Genomics (CCDGs) are conducting an in-depth genomics study of roughly 10 common diseases, including cardiovascular disease and developmental disorders, to identify genomic variants that either increase or decrease risk associated with those diseases. Using the generated data, the sites intend to develop improved and novel analysis methods and study designs across the entire program. So far, the CCDG sites have generated over 50,000 whole-genome sequences and over 38,000 whole-exome sequences (the protein-coding portions of the genome); the size of such studies is needed to generate the statistical power that will allow reliable conclusions about these diseases to be derived.

Many of NHGRI's principal accomplishments have centered on unraveling the complexities of the genome and giving researchers open access to valuable data. For example, the Encyclopedia of DNA Elements (ENCODE) Project is creating a catalog of all the parts of the human genome that are functional (i.e., that play an active biological role). All of the generated ENCODE data are made freely available, providing every scientist rapid access to this unique and valuable information for their research. In fact, ENCODE's value in biomedicine can be readily appreciated by the widespread use of these data: there are more than 2,000 scientific publications from research groups that have used ENCODE data for their published work.

Another treasure trove of data for the biomedical research community was generated by the NHGRI-led Common Fund project GTEx (genotype-tissue expression), which began in 2008 and

aimed to establish a database and accompanying tissue bank to allow scientists to study the relationship between genomic variation and gene expression. In October 2017, *Nature* published a collection of papers highlighting discoveries from the program. The analyses include data for thousands of tissue samples and demonstrated how gene regulation differs across individuals and tissue types.

NHGRI has also been building its portfolio in genomic medicine, piloting projects that seek to explore how to integrate genome sequencing within clinical care and begin to build an evidence base demonstrating its effectiveness. One example is the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, which began in 2013 to study the opportunities and challenges in the use of genome sequencing for the care of newborns. NSIGHT has shown ways in which newborn sequencing can be critical for saving lives by increasing the speed of diagnosis. For example, one of our NSIGHT grantees, whose work was recently featured in *Time* magazine, is using genome sequencing to provide diagnoses and suggest treatment changes for critically ill infants in the neonatal intensive care unit in a timeframe that can make life-altering differences.¹ Notably, this group recently set a Guinness World Record for the fastest genomic diagnosis—19.5 hours.

Conclusion

As is clear from our research portfolio, NHGRI does more than fund the discovery of knowledge and create new technology—we have catalyzed cultural changes across biomedical research. We have demonstrated an unrelenting commitment to data sharing, our ‘team science’ approach has fostered a spirit of collaboration among scientists, and we have provided researchers with access to shared tools and data to transform genomic advances into health discoveries. As NHGRI delves into strategic planning in FY 2019 and beyond, we will collaborate with experts in the field to identify the cutting-edge areas across our diverse research domains that the Institute should champion and support in the coming decade. We will also continue to tackle the underrepresentation of minorities in genomics research to be sure that the knowledge gained through the federal investment in genomics benefits all.

NHGRI believes that advances in genomics research are transforming our understanding of human health and disease, and we are excited to continue accelerating breakthroughs, improving patient care, and advancing genomics in society.

¹ Park, A. (2017) Genetic Testing is Providing New Hope for Babies Born with Mysterious Ailments. *Time*. <http://time.com/4951200/genetic-testing-providing-hope-babies-ailments/>

Eric D. Green, M.D., Ph.D.
Director, National Human Genome Research Institute

Eric D. Green, M.D., Ph.D. is the Director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH), a position he has held since late 2009. NHGRI is the largest organization in the world solely dedicated to genomics research. Previously, he served as the NHGRI Scientific Director (2002-2009), Chief of the NHGRI Genome Technology Branch (1996-2009), and Director of the NIH Intramural Sequencing Center (1997-2009).

Born and raised in St. Louis, Missouri, Dr. Green received his B.S. degree in Bacteriology from the University of Wisconsin-Madison in 1981, and his M.D. and Ph.D. degrees from Washington University in 1987. During residency training in clinical pathology (laboratory medicine), he worked in the laboratory of Dr. Maynard Olson, where he launched his career in genomics research. In 1992, he was appointed Assistant Professor of Pathology and Genetics as well as a Co-Investigator in the Human Genome Center at Washington University. In 1994, he joined the newly established Intramural Research Program of the National Center for Human Genome Research, later renamed the National Human Genome Research Institute.

While directing an independent research program for almost two decades, Dr. Green was at the forefront of efforts to map, sequence, and understand eukaryotic genomes. His work included significant, start-to-finish involvement in the Human Genome Project. These efforts eventually blossomed into a highly productive program in comparative genomics that provided important insights about genome structure, function, and evolution. His laboratory also identified and characterized several human disease genes, including those implicated in certain forms of hereditary deafness, vascular disease, and inherited peripheral neuropathy.

As Director of NHGRI, Dr. Green is responsible for providing overall leadership of the Institute's research portfolio and other initiatives. In 2011, Dr. Green led NHGRI to the completion of a strategic planning process that yielded a new vision for the future of genomics research, entitled *Charting a course for genomic medicine from base pairs to bedside* (*Nature* 470:204-213, 2011). Since that time, he has led the Institute in broadening its research mission; this has included designing and launching a number of major programs to accelerate the application of genomics to medical care. With the rapidly expanding scope of genomics, his leadership efforts have also involved significant coordination with multiple components of the NIH, as well as other agencies and organizations.

Beyond NHGRI-specific programs, Dr. Green has also played an instrumental leadership role in the development of a number of high-profile efforts relevant to genomics, including the Smithsonian-NHGRI exhibition *Genome: Unlocking Life's Code*, the NIH Big Data to Knowledge (BD2K) program, the NIH Genomic Data Sharing Policy, and the U.S. Precision Medicine Initiative.

**PREPARED STATEMENT OF GARY H. GIBBONS, M.D.
DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

This year, the NHLBI commemorates its 70th anniversary and a legacy of achievements across the broad spectrum of research – including basic science, epidemiology studies, implementation research, training, and landmark clinical trials – that have helped people all over the world live longer, healthier lives. Moving forward, the Institute remains committed to leveraging scientific opportunities and working in partnership with the public and private sector to prevent and treat heart, lung, blood, and sleep disorders.

INVESTING IN BASIC RESEARCH TODAY FOR TOMORROW'S CURES

The NHLBI's continued investments in fundamental discovery science provide the foundation for tomorrow's medical breakthroughs. This includes the NHLBI's support for research on the circadian rhythm (the body's daily internal clock), how it is regulated, and its relationship to the risk of chronic disease. Well known to cardiologists, blood pressure rises and falls on a daily rhythm, reaching its peak in the early morning – which is also when the risk for heart attacks and other cardiovascular events is greatest. Moreover, disruption of circadian rhythms has been shown to contribute to obesity, diabetes, and other conditions that can increase the risk of heart, lung, blood, and sleep disorders. Recent discoveries from basic research – including work on fruit flies recognized with the 2017 Nobel Prize in Medicine – have revealed new insights on the genetic and molecular pathways underlying circadian rhythms that are opening new doors to prevention and treatment.

To leverage these discoveries, the NHLBI has partnered with the National Institute of Diabetes and Digestive and Kidney Diseases on a program to better understand how circadian-dependent mechanisms contribute to obesity and to the risk of heart and lung disorders linked to obesity. Such research may help identify novel therapies that act on the circadian rhythm to prevent or manage these disorders.² As researchers learn more about the basic pathways underlying circadian function, they may also gain new insights into treating sleep disorders such as sleep apnea.

THE POWER OF DATA TO PERSONALIZE MEDICINE

The goal of precision medicine is to give health care providers the tools to better predict health and preempt chronic disease, and to tailor treatment strategies to a patient's unique characteristics. To accomplish this, the NHLBI's Trans-Omics for Precision Medicine (TOPMed) program is integrating clinical, genomic, and other data from diverse cohort studies, including the NHLBI's long-standing Framingham Heart Study and Jackson Heart Study, which continue to help us understand who is vulnerable to chronic diseases and why. To date, TOPMed has generated whole-genome sequences from 120,000 individuals in these studies, which we expect will identify new genetic risk factors for disease and new molecular targets for therapy.

Data from TOPMed will be included in a pilot of the new NIH Data Commons, a public-private partnership to bring research findings into a cloud-computing environment to enhance data

² <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-020.html>

sharing. This effort will give researchers access to data from hundreds of studies, creating new opportunities for collaborative research, innovation, and discovery.

REDUCING HEALTH DISPARITIES

Despite declines in overall death rates from cardiovascular disease (CVD), many populations in the United States, whether defined by race, gender, geography, or other factors, continue to experience a high burden of CVD and other chronic diseases. Increasingly, it is clear that place matters. Where people live, work, and play affects their susceptibility to disease and their health outcomes.

A 2017 study of more than 3,000 counties found a high burden of CVD throughout the U.S. heartland, from Kentucky to Oklahoma, with mortality rates in the highest-burden counties up to four times higher than in the lowest-burden counties.³ New CDC data also shows that rural Americans face a higher burden of chronic obstructive pulmonary disease (COPD) than urban Americans and are dying from it at higher rates.⁴ Many communities face economic, cultural, and geographic barriers to disease awareness, prevention, and treatment, reflected in a high burden of CVD risk factors such as high blood pressure, smoking, low physical activity, and high-calorie diets.

These data help inform efforts to reduce health disparities through implementation research. For example, a recent NHLBI-funded study shows the power of using non-traditional settings to adapt and implement health care interventions for high-risk communities. In the study, blood pressure screenings and pharmacist referrals at barbershops helped reduce high blood pressure among African American men in the Los Angeles area.⁵ In alignment with the comprehensive federal COPD National Action Plan, other research seeks to improve COPD care in medically underserved areas. One recent study found that a set of simple affordable diagnostic tools can help primary care providers identify patients with COPD and follow up with appropriate treatment.⁶

The NHLBI is expanding its implementation research programs. The STIMULATE initiative seeks investigator-initiated proposals to overcome barriers to implementation of proven interventions, and DECIPHeR will create opportunities to integrate intervention trials into the NHLBI's long-running observational studies of minority populations.

SICKLE CELL DISEASE: FROM BETTER TREATMENTS TO A CURE

While the NHLBI supports implementation research programs in sickle cell disease (SCD) that are helping develop and test approaches to improve patient outcomes, fundamental discoveries in stem cell biology and genomics are converging toward a cure. SCD is a genetic blood disorder that affects 100,000 Americans and millions worldwide. It is caused by a genetic mutation that causes the body's red blood cells to take on a sickled shape and obstruct blood flow, leading to severe frequent pain, organ damage, and other debilitating effects.

More than 50 percent of adults with SCD have significant pain more than three days per week, and about 40 percent take opioid pain medications daily. The NHLBI supports research to investigate mechanisms of pain in SCD and the potential for non-opioid treatments. This research will assist in addressing the Nation's devastating opioid epidemic, by helping ensure that individuals with SCD and other types of chronic pain can acquire effective relief without over-reliance on opioids.

³ <https://jamanetwork.com/journals/jama/fullarticle/2626571>

⁴ <https://www.cdc.gov/mmwr/volumes/67/wr/mm6707a1.htm>

⁵ <https://www.ncbi.nlm.nih.gov/pubmed/29527973>

⁶ <https://www.ncbi.nlm.nih.gov/pubmed/27783539>

In addition to managing pain and other complications of SCD, it is possible to cure SCD with a bone marrow transplant. However, this procedure requires that the patient have a healthy, immunologically matched marrow donor, which is not an option for most patients.

Advances in gene-editing technologies, such as CRISPR, are offering new hope for a cure that works for all patients. By using the patient's own bone marrow stem cells, researchers can replace the faulty SCD gene or edit the misspelled gene and transplant the corrected cells back into the patient, without the risk of immune rejection. NHLBI intramural scientists are leading cutting-edge research and clinical trials in this area.

Curing this disease within the decade is not something the NIH can do alone. The NHLBI Cure Sickle Cell initiative is bringing together patients, patient advocacy groups, health care providers, academic researchers, and industry to accelerate development of a widely available SCD cure.

CONCLUSION

Medical breakthroughs and improvements in public health that once seemed impossible are now within reach due in large part to the NHLBI's seven decades of investing in excellent science. The Institute remains committed to funding investigator-initiated discovery science, training and building a talented diverse scientific workforce to help address an array of research needs, forming new strategic partnerships, and promoting the implementation of evidence-based care. Through these multi-pronged efforts, the NHLBI will continue to stimulate the scientific advances needed to further reduce suffering from heart, lung, blood, and sleep disorders.

Gary H. Gibbons, M.D.
Director, National Heart, Lung, and Blood Institute

Gary H. Gibbons, M.D., is director of the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH), where he oversees the third largest institute at the NIH, with an annual budget of more than \$3 billion and a staff of about 900 federal employees. The NHLBI provides global leadership for research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives.

Since being named director of the NHLBI, Dr. Gibbons has enhanced the NHLBI investment in fundamental discovery science, steadily increasing the payline and number of awards for established and early stage investigators. His commitment to nurturing the next generation of scientists is manifest in expanded funding for career development and loan repayment awards, as well as initiatives to facilitate the transition to independent research awards.

Dr. Gibbons provides leadership to advance several NIH initiatives, and has made many scientific contributions in the fields of vascular biology, genomic medicine, and the pathogenesis of vascular diseases. His research focuses on investigating the relationships between clinical phenotypes, behavior, molecular interactions, and social determinants on gene expression and their contribution to cardiovascular disease. Dr. Gibbons has received several patents for innovations derived from his research in the fields of vascular biology and the pathogenesis of vascular diseases.

Dr. Gibbons earned his undergraduate degree from Princeton University in New Jersey, and graduated *magna cum laude* from Harvard Medical School in Boston. He completed his residency and cardiology fellowship at the Harvard-affiliated Brigham and Women's Hospital. Dr. Gibbons was a member of the faculty at Stanford University in California from 1990-1996, and at Harvard Medical School from 1996-1999. He joined the Morehouse School of Medicine in Atlanta in 1999, where he served as the founding director of the Cardiovascular Research Institute, chairperson of the Department of Physiology, and professor of physiology and medicine. While at Morehouse, Dr. Gibbons served as a member of the National Heart, Lung, and Blood Advisory Council from 2009-2012.

Throughout his career, Dr. Gibbons has received numerous honors, including election to the Institute of Medicine of the National Academies of Sciences; selection as a Robert Wood Johnson Foundation Minority Faculty Development Awardee; selection as a Pew Foundation Biomedical Scholar; and recognition as an Established Investigator of the American Heart Association.

**PREPARED STATEMENT OF RICHARD J. HODES, M.D.
DIRECTOR, NATIONAL INSTITUTE ON AGING**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute on Aging (NIA) of the National Institutes of Health (NIH).

AGING: A UNIVERSAL RISK FACTOR

Each one of us is susceptible to the effects of aging, which remains the most powerful driver of chronic diseases and disabilities that affect older adults. As the number of Americans ages 65 and older soars in the coming decades—from an estimated 46.2 million in 2014 to 82.3 million in just 26 years, according to projections from the U.S. Census Bureau—it is increasingly urgent that we pursue a comprehensive national effort to understand aging, to develop interventions that will help older adults enjoy robust health and independence, and to support American elders' active engagement with their families and communities.

At the NIH, the NIA leads this effort. We support genetic, biological, clinical, behavioral, and social research related to the aging process, healthy aging, and diseases and conditions that increase with age. We also support training of the next generation of researchers in geriatrics and related fields. In addition, we are the lead federal agency supporting research on Alzheimer's disease and related forms of dementia (AD/ADRD).

RESEARCH ON ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

In a recent analysis based on 2010 data, 5.5 million Americans were projected to have Alzheimer's disease by 2018. It's true that several studies, including the long-running Framingham Heart Study, have identified declines in the incidence and prevalence of dementia since the 1970s, possibly associated with increased educational attainment among study populations. However, if current population trends continue, these numbers will increase significantly as the number of older Americans rises—unless we learn how to prevent or effectively treat the disease.

Since passage of the National Alzheimer's Project Act in 2011, an extraordinary influx of funding directed at AD/ADRD has made it possible for NIH, led by NIA, to begin building a series of bold and innovative research programs, infrastructure, and new partnerships aimed at laying the foundation for precision medicine for AD/ADRD. NIA and other NIH Institutes are harnessing the tremendous power of big data to gain insight into the basic biology of AD/ADRD, as well as factors that may confer resilience to these diseases; accelerating the discovery of the next generation of new targets and biomarkers through the open science research model of the Accelerating Medicines Partnership for AD (AMP-AD); and establishing new translational infrastructure programs to enable rapid sharing of data and research models and enhancing research rigor and reproducibility.

NIA currently supports over 140 active clinical trials of interventions to enhance cognitive health in older individuals and to prevent, treat, or manage symptoms of AD/ADRD. These studies range from studies of emerging therapeutics developed in academic centers and the small business community, to studies of the cognitive effects of drugs commonly used for other conditions, to clinical trials involving lifestyle interventions such as exercise, dietary change, and cognitive training. Investigators with AMP-AD have identified over 100 potential new drug targets for AD/ADRD, and over 30 projects for development of novel therapeutics against a variety of targets are under way in NIA's Alzheimer's Disease Translational Research Program. NIH has also established the Alzheimer's Clinical Trial Consortium (ACTC), consisting of 35 sites across the United States, to support trials across the full spectrum of AD/ADRD. The ACTC will also spur innovation in trial design and recruitment, with a specific focus on inclusion of communities underrepresented in AD research.

We have made important progress. For example, an NIA-supported international research team used cryo-electron microscopy to visualize the structure of individual tau fibrils (a pathological hallmark of several forms of dementia) for the first time. The high-resolution, exquisitely detailed images helped explain why tau-based therapies have been difficult to develop—its components are so tightly bound together as to be impermeable—but also suggested possible new avenues for therapy. Other investigators analyzed Medicare data and noted an association between use of cholesterol-lowering statin drugs and reduced risk of AD. Intriguingly, the reduction in risk varied across sex, race, and particular statin used, suggesting that the right statin type for the right person at the right time may provide a relatively inexpensive means to lessen the burden of AD.

Our continuing efforts have been informed by input from researchers and advocates worldwide through key scientific conferences, including periodic Summits on Alzheimer's Disease (most recent: March 2018) and Alzheimer's Disease-Related Dementias (most recent: 2016, with the next Summit planned for 2019). A Summit in October 2017 also brought together experts to discuss dementia care and the unique needs of caregivers of persons with AD/ADRD.

ADVANCING AGING RESEARCH

Recognizing aging as the most powerful risk factor for diverse diseases and frailties, NIA supports research into the underlying biological mechanisms of aging. For example, the trans-NIH Geroscience Interest Group, established by the NIA and joined by most NIH Institutes, promotes research on the links between aging biology and etiology of chronic diseases. NIA also supports research on diet and healthy aging, as well as two multi-investigator interventions testing programs to identify and validate compounds that extend life and improve health in laboratory animals. Ongoing collaborations with the National Institute of Allergy and Infectious Diseases and the National Cancer Institute continue to expand our understanding of the aging immune system and the role of aging in the etiology of cancer.

NIA's longtime flagship studies in aging remain vibrant with opportunities to apply new technologies and thinking to their treasure troves of data. The Baltimore Longitudinal Study on Aging, sixty years old in 2018, continues to break new ground in identifying the longitudinal physical and cognitive changes that define aging; elucidating the factors that affect the rate of

age-related change; and understanding the relationship between advancing age and chronic disease. BLSA investigators are particularly interested in “exceptional agers” – those rare individuals who live well into their eighties with few health problems. This year the Health and Retirement Study (HRS) will complete 25 years of data collection and will mark the occasion with several enhancements, including deployment of an improved approach to assessing cognitive impairment and dementia and expanded collection of objective health measures, including blood-based assays capturing the aging of the immune system and related molecular and cellular age-related changes. This project and others are designed to reveal the biological pathways through which differences among social and demographic groups can affect health.

NIA-supported investigators are looking at better ways to translate what we know into clinical practice that will help improve the health and well-being of older Americans. For example, starting in FY 2019, NIA will support demonstration projects leading to pragmatic trials—clinical trials that are conducted under “real-world” conditions, as opposed to the tightly controlled conditions of a traditional trial—for a variety of age-related diseases and conditions, including care of persons with dementia in long-term settings. The National Advisory Council on Aging has also recently approved in concept a new initiative to explore “deprescribing” strategies for older adults with multiple chronic health conditions. This research, which will begin in FY 2019, will address inappropriate prescribing of medication, which is estimated to affect 20 percent of older adults, one-third of individuals in long-term care facilities and over half of the persons with advanced dementia in nursing homes.

EMPOWERING THE NEXT GENERATION OF SCIENTISTS

As the number of older Americans continues to grow, we must foster the development of the next generation of scientists whose research will lead to improved care and more effective treatment for older patients with complex medical conditions. To encourage emerging scientists, NIA supports an advantage in pay line for new and early-stage investigators. The Paul Beeson Career Development Awards in Aging Research program, sponsored by the NIA, the National Institute of Neurological Disorders and Stroke, and private partners, continues to produce leaders in the fields of aging and geriatrics research. A recent Funding Opportunity Announcement led to awards for four new training programs for joint MD-PhDs in the social sciences relevant to aging. Finally, the Butler-Williams Scholars Program (formerly the NIA Summer Institute) remains a vibrant and vital institution at NIA.

Thank you. I welcome your questions.

Richard J. Hodes, M.D.

Director, National Institute on Aging (NIA), National Institutes of Health (NIH)

Richard J. Hodes, M.D., is the Director of the National Institute on Aging (NIA) at the National Institutes of Health (NIH). Dr. Hodes, a leading researcher in the field of immunology, was named to head the NIA in 1993.

The NIA leads the Federal effort supporting and conducting research on the biological, clinical, behavioral and social aspects of aging. Dr. Hodes has devoted his tenure to the development of a strong, diverse, and balanced research program. This has led to new and innovative ways to conduct research, share data and translate findings into practice. Basic biologic research is examining genetic and other factors influencing aging, how they affect longevity and the development of age related diseases. Research in geriatrics is uncovering new ways to combat frailty and improve function with age. Behavioral and social research is deepening understanding of the individual behaviors and societal decisions that affect well-being.

Dr. Hodes also directs the Federal effort to find effective ways to treat or prevent Alzheimer's disease, as the NIA is the lead NIH institute for this mission. Cutting edge research conducted and supported by the NIA, often in collaboration across institutes at the NIH, has helped to revolutionize the way we think about Alzheimer's disease and related dementias. Studies in genetics, basic mechanisms, imaging and biomarkers have spurred the development of potential therapies aimed at a variety of targets and the testing of interventions at the earliest signs of disease.

Dr. Hodes' research laboratory in the National Cancer Institute focuses on the cellular and molecular mechanisms that regulate the immune response. Additional background is available at the lab's website⁷.

A graduate of Yale University, Dr. Hodes received his M.D. from Harvard Medical School. He is a Diplomate of the American Board of Internal Medicine, a member of The Dana Alliance for Brain Initiatives, a Fellow of the American Association for the Advancement of Science, and a member of the National Academy of Medicine of the National Academies.

⁷ <http://ccr.cancer.gov/Staff/Staff.asp?StaffID=472A>

**PREPARED STATEMENT OF GEORGE F. KOOB, PH.D.
DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health (NIH).

BURDEN OF ALCOHOL MISUSE IN THE UNITED STATES

Alcohol misuse has profound effects on the health and well-being of individuals, families, and communities. Approximately 15 million people in the United States have alcohol use disorder (AUD), a chronic relapsing brain disease related to alcohol misuse. 88,000 lives are lost to alcohol-related causes annually, making alcohol the third leading preventable cause of death in the United States. Alcohol misuse cost the U.S. almost \$250 billion in 2010. Guided by its 2017-2021 strategic plan, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports research and initiatives to generate and disseminate fundamental knowledge about the effects of alcohol on health and well-being, and apply that knowledge to improve the diagnosis, prevention, and treatment of alcohol-related problems, including AUD, across the lifespan.

ADVANCING TRANSLATIONAL AND CLINICAL RESEARCH

For nearly five decades, NIAAA has supported cutting-edge research to reduce the toll that alcohol misuse takes on human health and well-being. The Institute's vast portfolio of translational and clinical research has led to more effective interventions to prevent and treat alcohol misuse and related conditions, provided support for integrating prevention and treatment services into mainstream health care, and paved the way for the development of novel strategies to address medical conditions associated with alcohol misuse.

Alcohol Treatment NavigatorSM

In any given year, less than 10 percent of individuals diagnosed with AUD receive treatment. Although effective behavioral interventions and medication-assisted treatment are available, in addition to mutual help groups, people often do not know the full extent of their options or where to turn for help. In October 2017, NIAAA launched the Alcohol Treatment NavigatorSM (alcoholtreatment.niaaa.nih.gov), a comprehensive online resource to help people search for professionally-led, evidence-based alcohol treatment. The Navigator educates consumers about AUD and treatment options, provides 10 recommended questions to ask a potential provider, and suggests five signs of higher quality treatment to recognize. It also provides instructions for searching several existing online directories of licensed professional therapists, accredited alcohol treatment programs, and board-certified addiction medicine physicians. With the Navigator, adults searching for AUD treatment will be better able to find care that meets their unique needs, friends and family members will feel empowered to help an adult loved one struggling with AUD, and health care providers can feel more confident in screening their patients for AUD knowing there is a tool to share with those who need a referral to treatment. Given that treatments for AUD work better for some people than others, NIAAA will continue to support research on the neurobiological mechanisms that underlie AUD to

identify novel medication targets that could ultimately expand the number of effective treatment options.

Addiction medicine in routine health care

Many individuals with AUD often seek primary care for a health problem related to alcohol misuse rather than for the misuse itself, indicating a need for addiction medicine approaches in routine medical practice. NIAAA provides primary care and other health care providers with tools to help them become more proficient in conducting alcohol screening and evidence-based interventions, including medication-assisted treatment. The Institute is also partnering with the National Institute on Drug Abuse, the Substance Abuse and Mental Health Services Administration, and others to improve physician training in the diagnosis, prevention, and treatment of alcohol and other substance misuse and to expand the range of health care providers appropriately trained in identifying and addressing these problems.

Alcohol-associated liver diseases

In the United States, about half of liver disease deaths are attributable to alcohol misuse. NIAAA will continue to invest in clinical and translational research to develop treatments for alcohol-associated liver diseases such as alcoholic hepatitis, a deadly form of liver disease for which there are no treatments approved by the Food and Drug Administration (FDA). The Institute aims to strengthen its research programs in alcoholic hepatitis through the establishment of a clinical and translational network to streamline the design, initiation, and conduct of clinical trials, reduce administrative redundancy, and optimize the use of scientific innovations. NIAAA is collaborating with the FDA to identify appropriate clinical trial endpoints for studies investigating novel treatments for alcohol-associated liver diseases as well as safe, effective therapies for AUD in liver disease patients.

Fetal Alcohol Spectrum Disorders

Prenatal alcohol exposure is a leading preventable cause of developmental abnormalities that contribute to a broad range of lifelong physical, cognitive, and behavioral challenges known as Fetal Alcohol Spectrum Disorders (FASD). Among NIAAA's extensive portfolio in FASD research are studies to establish more accurate FASD prevalence estimates. A new NIAAA-supported study of more than 6,000 first-graders across four U.S. communities (Midwest, Rocky Mountain, Southeast and Pacific Southwest) has found that as many as 1-5 percent of first-grade children have FASD. This finding provides further evidence that FASD is a significant public health problem in the U.S. and strategies to expand screening, diagnosis, prevention, and treatment in communities are needed to address it.

EMERGING PUBLIC HEALTH ISSUES

Changing patterns in alcohol consumption, shifts in the burden of alcohol-related disease, and shifts in the demographic composition of the U.S. pose new challenges for alcohol prevention and treatment. Identifying and addressing emerging public health issues early can lessen the societal burden and associated costs.

Increases in alcohol-related emergency department visits

A new study found that the rate of alcohol-related emergency department visits in the U.S. increased by nearly 50 percent between 2006-2014, especially among women and older adults. About 15 percent of the visits involved substances in addition to alcohol. Alcohol interacts with a variety of prescription and illicit drugs, including opioid pain relievers, which dramatically increase the risk of overdose deaths and may partially explain the increased prevalence of emergency department visits also observed for alcohol and medication interactions. The relationship between alcohol and pain is another area of interest including how chronic alcohol misuse increases sensitivity to pain, and how pain drives alcohol misuse. NIAAA is supporting epidemiological studies to determine the associations between alcohol and opioid misuse as well as basic research to elucidate the neurobiological mechanisms through which alcohol, opioids, and pain interact.

Extreme binge drinking

A recent NIAAA study based on 2012-2013 data found that that nearly 32 million adults in the U.S. (13 percent of the population aged 18 and older) engaged in extreme binge drinking, i.e., consuming alcohol at levels two or more times the binge thresholds, in the past year. Extreme binge drinking was associated with an elevated likelihood of emergency department visits and other adverse consequences. NIAAA is forming a working group of external experts to better understand the social and cultural determinants of extreme binge drinking to inform the development of improved interventions.

Alcohol misuse among women

A growing body of evidence indicates that women who drink are at increased susceptibility to short- and long-term alcohol-related consequences, and alcohol use and misuse are increasing more significantly among women than men. NIAAA encourages basic, clinical, and translational research on the biological bases of sex differences in the development of AUD and associated consequences, factors that increase risks for AUD and co-occurring disorders, and improved diagnosis and evidence-based interventions that consider the unique needs of women.

Alcohol misuse among older adults

As people age, they tend to be more sensitive to alcohol's effects, and are more likely to experience health conditions exacerbated by alcohol misuse as well as alcohol-medication interactions. An analysis of data from 1997-2014 showed an increase in drinking and binge drinking among adults aged 60 and older, particularly among women. NIAAA-supported studies are focused on identifying and reducing unhealthy alcohol use among older adults as well as elucidating how alcohol contributes to age-related changes in the brain. For example, a recent study of older adults with AUD has shown accelerated declines in various brain regions and circuits, including in the frontal cortex which may lead to accelerated impairments in cognitive function.

CONCLUSION

Advances in alcohol research have expanded our knowledge of the effects of alcohol on health and resulted in numerous evidence-based preventive and treatment interventions. Still, more work needs to be done to reduce the burden of alcohol misuse in our Nation. With its FY

2019 budget, NIAAA will continue to invest in basic, clinical, and translational research to address existing and emerging public health concerns and cultivate the biomedical research workforce to harness the contributions and perspectives of the broadest range of investigators.

George F. Koob, Ph.D.
Director, National Institute on Alcohol Abuse and Alcoholism

George F. Koob, Ph.D., is an internationally-recognized expert on alcohol and stress, and the neurobiology of alcohol and drug addiction. As NIAAA Director, Dr. Koob oversees a broad portfolio of alcohol research ranging from basic science to epidemiology, diagnostics, prevention, and treatment.

Dr. Koob earned his doctorate in Behavioral Physiology from Johns Hopkins University in 1972. Prior to taking the helm at NIAAA, he served as Professor and Chair of the Scripps' Committee on the Neurobiology of Addictive Disorders and Director of the Alcohol Research Center at the Scripps Research Institute. Early in his career, Dr. Koob conducted research in the Department of Neurophysiology at the Walter Reed Army Institute of Research and in the Arthur Vining Davis Center for Behavioral Neurobiology at the Salk Institute for Biological Studies. He was a post-doctoral fellow in the Department of Experimental Psychology and the MRC Neuropharmacology Unit at the University of Cambridge.

Dr. Koob began his career investigating the neurobiology of emotion, particularly how the brain processes reward and stress. He subsequently applied basic research on emotions, including on the anatomical and neurochemical underpinnings of emotional function, to alcohol and drug addiction, significantly broadening knowledge of the adaptations within reward and stress neurocircuits that lead to addiction. This work has advanced our understanding of the physiological effects of alcohol and other substance use and why some people transition from use to misuse to addiction, while others do not. Dr. Koob has authored more than 700 peer-reviewed scientific papers and is a co-author of *The Neurobiology of Addiction*, a comprehensive textbook reviewing the most critical neurobiology of addiction research conducted over the past 50 years.

Dr. Koob is a member of the National Academy of Medicine and the recipient of many other prestigious honors and awards recognizing his scientific contributions, including the Legion of Honor from the government of France; the Seixas, Distinguished Investigator, and Marlatt Mentorship awards from the Research Society on Alcoholism; the Daniel Efron Award and the Axelrod Mentorship Award, both from the American College of Neuropsychopharmacology; the NIAAA Mark Keller Award; and the Neuronal Plasticity Prize from the La Foundation Ipsen.

**PREPARED STATEMENT OF ANTHONY S. FAUCI, M.D.
DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

NIAID has a dual mandate to maintain and grow a robust basic and clinical research portfolio in the areas of microbiology, infectious diseases, immunology, and allergy as well as to launch a swift research response when infectious diseases emerge and re-emerge. NIAID makes vital contributions to developing diagnostics, therapeutics, and vaccines by supporting medical countermeasures specific to single pathogens as well as platform technologies that can be deployed to target multiple pathogens. Also, NIAID research that has responded to ongoing public health threats has been a key component of U.S. biodefense preparedness.

RESEARCH ON INFECTIOUS DISEASES

Influenza, Including Universal Influenza Vaccine Development. NIAID supports basic, translational, and clinical research to address the constant threat of seasonal and pandemic influenza. Concerns over the efficacy of seasonal influenza vaccine, and the threat of pandemics such as posed by H7N9 influenza, highlight the need for a new generation of influenza vaccines. NIAID recently convened influenza research experts from around the world at a workshop that led to the development of a Strategic Plan for a Universal Influenza Vaccine. NIAID's Strategic Plan outlines research priorities in three areas important for understanding the formidable challenges posed by influenza and advancing the development of universal influenza vaccines. These research areas are: 1) transmission, natural history, and pathogenesis of influenza infection; 2) influenza immunity and factors correlated with immune protection; and 3) vaccine approaches to elicit broad, protective immune responses.

NIAID is pursuing the research agenda outlined in the Strategic Plan, including research on cohorts of infants to determine how influenza vaccinations and natural influenza infections may affect immunity to influenza infection or immunization later in life. These cohort studies will provide vital information to facilitate the design of broadly protective influenza vaccines. NIAID also is supporting the development of several universal influenza vaccine candidates. One strategy pursued by NIAID Vaccine Research Center scientists uses a platform to display portions of an influenza surface protein – hemagglutinin – that do not easily mutate and are relatively constant among influenza strains. A separate NIAID-supported approach uses non-infectious virus-like particles that display four types of influenza hemagglutinin in one vaccine. Another NIAID-funded strategy employs several influenza fragments recognized by the immune system that are common to different influenza virus strains. Each of these vaccine strategies aims to produce broad and durable immune responses that would be effective against multiple influenza strains.

Zika. NIAID research has led to the rapid development of diagnostics, candidate vaccines, and therapeutics to address the public health threat of Zika virus disease, especially Zika virus-related congenital abnormalities. NIAID scientists developed a DNA-based Zika vaccine that is now being tested in a large-scale clinical trial in Zika-endemic regions. NIAID is developing other candidate Zika vaccines, including a live, attenuated vaccine that targets both Zika virus and the related dengue virus. In addition, NIAID is partnering with other NIH Institutes and the Fiocruz Institute in Brazil to support the Zika in Infants and Pregnancy cohort study, which is assessing the risks of Zika infection in expectant mothers and tracking infant outcomes for at least one year.

Other Vector-borne Diseases. NIAID supports research to address mosquito-borne diseases such as dengue, malaria, chikungunya, and yellow fever, and tick-borne diseases such as Lyme disease. NIAID scientists developed a candidate dengue vaccine, TV003, that targets all four sub-types of dengue virus. TV003 currently is being tested in a large-scale clinical trial in Brazil. An NIAID-supported malaria vaccine, PfSPZ, contains a weakened form of the mosquito-borne malaria parasite. Recent clinical trials showed PfSPZ protects people against multiple malaria strains and prevents infection in a malaria-endemic region. NIAID also is supporting a clinical trial of a vaccine designed to trigger an immune response to mosquito saliva. This vaccine aims to prevent multiple mosquito-borne diseases by blocking their transmission from infected mosquitoes.

HIV/AIDS. NIAID research has led to powerful HIV treatment and prevention tools that improve the lives of individuals living with HIV and that have the potential to eventually end the HIV/AIDS pandemic. NIAID is supporting new HIV vaccine studies, including the Imbokodo trial in sub-Saharan Africa that is evaluating a vaccine candidate designed to protect against multiple global HIV strains. NIAID also is developing broadly neutralizing antibodies that can block most subtypes of HIV found worldwide. VRC01 is one such antibody that is currently being evaluated by passive infusion in two ongoing HIV prevention trials in individuals at high risk of HIV infection. Another broadly neutralizing antibody protected against infection in a monkey model of HIV. Further study in this model showed that a mixture of two broadly neutralizing antibodies could treat already infected animals. Enabled by the HOPE Act, NIAID also is building on its pioneering clinical trials of organ donation between HIV-infected individuals by launching a multi-site clinical trial of kidney transplantation in this population. NIAID continues to pursue additional methods to combat HIV, including microbicide-based approaches such as a vaginal ring infused with an anti-HIV drug, and long-acting injectable drugs to prevent and treat HIV.

Tuberculosis. NIAID supports research to address tuberculosis (TB) including the challenges of TB/HIV co-infection and increasing drug resistance. NIAID also leads the research component of the National Action Plan for Combating Multidrug-Resistant TB. NIAID scientists and collaborators have developed a new diagnostic tool that detects resistance to key antibiotics used to treat TB and may facilitate a point-of-care diagnostic approach to guide TB therapy. In addition, an NIAID clinical trial of HIV-infected individuals demonstrated that a one-month course of preventive TB medication was as safe and effective as a nine-month

regimen. Patients were more likely to complete the short regimen, suggesting it may be a preferred TB prevention strategy.

Antimicrobial Resistance. NIAID plays a critical role in research components of the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB). NIAID is collaborating with the Biomedical Advanced Research and Development Authority (BARDA) on the CARB Biopharmaceutical Accelerator, or CARB-X, a global public-private partnership to advance the preclinical and early clinical development of promising antibacterial drugs and other products. In addition, NIAID funds multiple clinical trials to evaluate novel antibiotics or optimize the use of current antibiotics. One recent study found that two common, inexpensive antibiotics can effectively treat methicillin-resistant *Staphylococcus aureus* skin abscesses. NIAID also supports clinical trials to develop zoliflodacin, a novel antibiotic for gonorrhea, an increasingly drug-resistant infection.

RESEARCH ON IMMUNOLOGY AND IMMUNE-MEDIATED DISORDERS

NIAID research has led to transformational advances in our understanding of the immune system and to new ways of treating and preventing immune-mediated diseases. For example, NIAID research on mechanisms of T-cell activation led to the development of “checkpoint inhibitors,” a new class of immunotherapy drugs for cancer.

Food Allergy. NIAID research investments have led to important advances in the prevention and treatment of food allergies. NIAID convened an expert panel to build on the findings of pivotal food allergy studies by developing new clinical guidelines to help prevent peanut allergy in at-risk infants. NIAID-supported researchers also have found that combining oral immunotherapy with the asthma drug omalizumab may be an effective strategy to simultaneously desensitize children with multiple food allergies.

Stem Cell Transplants for Treatment of Autoimmune Diseases. Two recent NIAID-supported clinical trials found that intensive immunosuppression followed by transplantation of a patient’s own stem cells was an effective treatment for progressive and life-threatening autoimmune diseases. The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial showed that stem cell transplantation improves survival and quality of life for people with severe scleroderma when compared with routine immunosuppression. The HALT-MS trial demonstrated sustained remission in most people with relapsing-remitting multiple sclerosis for five years following transplantation.

CONCLUSION

NIAID research continues to drive rapid progress in the development of vaccines, therapeutics, and diagnostics that improve human health and enhance our ability to respond rapidly to emerging and re-emerging infectious diseases. NIAID-supported science and innovation will continue to pave the way to solutions for many of the formidable health challenges facing the Nation and the world.

Anthony S. Fauci, M.D.
Director, National Institute of Allergy and Infectious Diseases

Anthony S. Fauci, M.D., is a physician-scientist who directs the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health in Bethesda, Maryland. He oversees an extensive research program on infectious diseases such as HIV/AIDS, influenza, tuberculosis, Ebola and Zika, as well as diseases of the immune system. Dr. Fauci also serves as one of the key advisors to the White House and Department of Health and Human Services on global infectious disease issues. He was one of the principal architects of the President's Emergency Plan for AIDS Relief (PEPFAR), a program that has saved millions of lives throughout the developing world.

Dr. Fauci is the long-time chief of the NIAID Laboratory of Immunoregulation where he has made numerous important discoveries related to HIV/AIDS and is one of the most-cited scientists in the field. He is a member of the US National Academy of Sciences and the US National Academy of Medicine, and has received numerous prestigious awards for his scientific and global health accomplishments, including the National Medal of Science, the Robert Koch Medal, the Mary Woodard Lasker Award for Public Service, and the Presidential Medal of Freedom. He has been awarded 43 honorary doctoral degrees and is the author, coauthor, or editor of more than 1,300 scientific publications, including several major textbooks.

**PREPARED STATEMENT OF STEPHEN I. KATZ, M.D., Ph.D.
DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL
AND SKIN DISEASES**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH).

NIAMS RESEARCH IMPACTS EVERYONE

NIAMS is the primary Federal agency for supporting medical research on diseases of the bones, joints, muscles, and skin. As such, our work touches the lives of nearly every American. A 2018 publication by the Centers for Disease Control and Prevention notes that an estimated 23 percent (54 million) of Americans have been diagnosed with some form of arthritis, including osteoarthritis, rheumatoid arthritis, gout, and fibromyalgia; 24 million of whom have symptoms severe enough to hinder activities they want or need to do. This problem is expected to grow as our population ages; 78.4 million adults will have arthritis by 2040 if current trends continue. When arthritis is combined with other bone and joint conditions such as neck and low back pain, osteoporosis, and musculoskeletal injuries, the total cost of medical care and lost wages is estimated to be \$874 billion annually. Diseases in the NIAMS research portfolio also have a global impact. In 2015, low back and neck pain was the leading cause of disability worldwide, while skin diseases such as eczema and psoriasis ranked fifth.

NIAMS is enhancing health, lengthening life, and reducing illness and disability by supporting basic and translational research and clinical trials that will inform medical practice; training the next generation of bone, joint, muscle, and skin scientists; and disseminating health information and the findings from the studies it supports to all Americans. For the remainder of my statement, I will describe a few of the many recent research activities that are benefiting people today and enabling future advances.

RESEARCH ADVANCES FUNDED BY NIAMS

My first two examples focus on the risks and benefits of steroids, which an estimated one percent of the entire U.S. population takes as chronic therapy. A team of researchers studying the effects of repeated steroid injections for knee pain found that people who received shots every twelve weeks for two years showed worsening joint damage and no long-term reduction in pain compared with those who received saline injections. While this study did not evaluate the benefits of steroid injections into the knee for short-term pain relief, it does not support their long-term use for treatment of symptomatic knee osteoarthritis. Another group of investigators looked at the mechanisms by which steroids preserve muscle function for boys who have Duchenne muscular dystrophy. Using cells and a mouse model, the team determined that a weekly dosing regimen increases the activity of two genes involved in muscle cell repair, while daily dosing activates pathways that cause muscle to shrink and weaken. Their discovery explains the seemingly contradictory results of previous studies into the drugs' effects. If these observations from cell cultures and mice also occur in patients, this study could directly inform

how steroids are prescribed to maximize their therapeutic benefits while minimizing their negative effects.

After decades of investigating Pompe disease, a rare, life-threatening condition that cripples the muscles, NIAMS-funded researchers have developed a gene-transfer approach that shows promise in mice. While the study's main goal was to test whether the strategy would prevent the animals from developing an immune response, it also demonstrated that this gene therapy could potentially replace standard care. These results directly contributed to an investigational new drug approval by the Food and Drug Administration to move this approach into clinical trials. Gene therapy also holds promise for people who have the rare and life-threatening skin disease recessive dystrophic epidermolysis bullosa, which causes fragile, blistering skin. In a phase 1 clinical trial, investigators collected skin biopsies from four patients and used a harmless virus to correct the gene for the defective skin protein in the patients' cells. Next, they coaxed the genetically modified cells to grow into sheets of skin about the size of a deck of playing cards. Then, the new skin was grafted back onto patients to speed healing of the open wounds that characterize the disease. After 12 months, half of the two-dozen grafts were still covering patients' wounds. Investigators will continue monitoring these patients and are recruiting people for a phase 2 clinical trial.

NIAMS research is also developing techniques to help clinicians identify which patients are likely to have more severe or rapidly progressing disease. For example, researchers found that positron emission tomography (PET), a technique that can visualize the body's metabolic processes, could be used to distinguish between patients who have large vessel vasculitis or other diseases with similar symptoms. PET may also help clinicians predict which patients are at highest risk of disease relapse. Another study examined children with juvenile myositis, a disease where the muscles are attacked by antibodies in the patients' blood. The investigators found that children with a certain type of antibody experience worse muscle disease and more severe weakness. This finding also explains why these children show less benefit from existing therapies and opens a possibility for better treatments. Other researchers discovered blood markers that may distinguish the subset of people who have systemic sclerosis that are at risk of developing interstitial lung disease (the leading cause of death for these patients). This advance also may lead to new therapies.

Other studies of basic cellular processes hold promise for people who suffer from skin diseases. Investigators determined that a molecular pathway involving the protein JAK1 is involved in chronic itch. They then tested whether an existing drug that blocks JAK signaling could help people who do not respond to other treatments (e.g., some cases of atopic dermatitis). Their results were promising although further clinical studies are needed to confirm the findings. Additional teams of researchers are examining how microbes on the skin may influence a person's susceptibility to atopic dermatitis. A pair of studies, focusing on the role of the bacterium *Staphylococcus aureus* in driving the disorder, suggest that reducing *S. aureus* by increasing beneficial skin bacteria could be an effective treatment.

NIAMS-funded research is also having an impact beyond arthritis and musculoskeletal and skin diseases. For example, psoriasis has been linked to an increased risk of developing type 2 diabetes. A new finding that the risk of diabetes is highest for those with the most severe psoriasis sheds light on the causes of both diseases and provides compelling evidence that certain patients should receive targeted diabetes prevention strategies. Other investigators are showing

that while early antiretroviral therapy saves HIV patients' lives, it also damages their bones, emphasizing the importance of developing bone-preserving strategies for this population. Weight loss due to bariatric surgery, another life-saving intervention, also is associated with bone loss, and researchers are beginning to understand the role that glucose metabolism plays in bone health. This discovery could lead to targeted prevention and treatment strategies for osteoporosis, the skeletal complications of bariatric surgery, and diabetic bone fragility. Still other research is explaining why muscle breaks down in cancer patients (a process known as cachexia). A number of molecular pathways and targets underlying the muscle wasting process have been discovered recently, and investigators are beginning to identify existing drugs or new targets to stop this from occurring.

LOOKING TO A PROMISING FUTURE

The wide reach of NIAMS-funded research is allowing people affected by diseases within our mission to benefit from large multi-agency programs such as the Cancer Moonshot Program and the Regenerative Medicine Innovation Project supported by the 21st Century Cures Act. Moving forward, investigators will examine connections between immunotherapies for cancer and autoimmune disease and will continue to be encouraged to apply for funding for research on bone, joint, muscle, and skin regeneration. NIAMS, along with the National Institute of Allergy and Infectious Diseases, continues to lead the Accelerating Medicines Partnership (AMP) in rheumatoid arthritis and lupus which is working to identify and validate promising biological targets for those diseases. With guidance from NIAMS, three other Institutes, and the NIH Common Fund, the trans-NIH Molecular Transducers of Physical Activity in Humans program continues to make progress developing a database that researchers can use to elucidate changes that take place in our bodies in response to exercise and how those changes relate to human health.

In FY 2019, NIAMS plans to continue support for its Research Innovations for Scientific Knowledge (RISK) funding opportunities, which allow investigators from around the country to submit cutting edge, unconventional, innovative research proposals for up to three years of funding. To help bolster the next generation of researchers, the Institute also continues to encourage early established investigators who have successfully renewed their first NIAMS research project grant to apply for a supplemental funding program to aid the transition of their individual research project into a broader, more robust and resilient research program.

STEPHEN I. KATZ, M.D., Ph.D.
DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND
SKIN DISEASES

Stephen I. Katz, M.D., Ph.D., is Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, a position he has held since August 1995. He was also a Senior Investigator and Chief of the Dermatology Branch of the National Cancer Institute. Dr. Katz has focused his studies on immunology and the skin. He trained many outstanding immunodermatologists in the United States, Japan, Korea, and Europe. He has served many professional societies in leadership positions, including as Secretary-General of the 18th World Congress of Dermatology in New York in 1992, and as President of both the International League of Dermatological Societies and the International Committee of Dermatology and the Society for Investigative Dermatology. He has received many honors and awards, including the prestigious U.S. Distinguished Executive Presidential Rank Award.

**PREPARED STATEMENT OF JILL HEEMSKERK, PH.D.
ACTING DIRECTOR, NATIONAL INSTITUTE OF BIOMEDICAL
IMAGING AND BIOENGINEERING**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH).

The mission of NIBIB is to improve human health by leading the development of biomedical technologies and accelerating their application. NIBIB supports research that integrates engineering with the physical and life sciences to develop emerging technologies that can be applied to a broad range of biomedical and health care problems. Building partnerships with industry, academia, and other federal agencies is a high priority for the institute. A few examples from the many exciting NIBIB-funded research efforts that are leading to better, faster, and less costly ways to advance public health are shared in this testimony.

ON THE SPOT FOOD ALLERGY TESTING

Eating out can be a challenge for people with allergies. Diners must rely on knowing what ingredients contain the allergens they must avoid, and on restaurants to serve dishes that exclude them. Recognizing this widespread public health problem, researchers have developed a system called integrated exogenous antigen testing (iEAT). The purpose of the iEAT system is to give those who suffer from food allergies a rapid, accurate device that allows them to personally test foods in less than 10 minutes. The device is small enough to fit on a keychain and can test for common allergens such as gluten, milk, or nuts. The device contains a disposable testing chamber, so once a test is completed the chamber can be replaced and the device used again. After developing and testing a prototype of the device, the research team granted a license to a local start-up company to make iEAT commercially available. In the future the device could be adapted to test for other allergens or substances.

CUFF-LESS BLOOD PRESSURING MONITORING

A person's blood pressure is one of several key indicators of health, but the inflatable cuff device used to measure blood pressure is largely the same as it was 100 years ago. Measuring blood pressure while in a doctor's office gives physicians a limited view since blood pressure can vary throughout the day. Researchers are developing a new "cuff-less" method to accurately measure blood pressure more frequently and without the need for special equipment. One group is making progress using a modified smart phone case with built-in sensors and an app to capture blood pressure by pressing a finger on the phone's home button. The ability to monitor blood pressure on an ongoing basis could help alert people to potential problems and more consistently monitor their blood pressure if they are at risk or are taking medications. This could help reduce the risk of cardiovascular disease through improved management of blood pressure.

CLEARING OUT BLOOD CLOTS

Blood clots that form in the deep veins of the legs are called deep vein thrombosis and can be quite painful, and even fatal if a clot dislodges from the wall of the vein and travels to the heart or lungs. Currently, intravascular treatments use devices inserted into the vein to trap clots, but they have limitations including damage to the blood vessel wall. In some patients, clot-thinning medication is required, which can have a range of side effects. A new approach to overcome these limitations uses a surgical tool that is inserted into a vein and directs ultrasound waves directly at clots to break them up into tiny pieces. It is targeted and therefore minimizes damage to blood vessels; and because the broken pieces are tiny, patients do not need to use blood thinning medication following the procedure. In addition to using ultrasound, researchers are adding injectable microbubbles that vibrate when exposed to the ultrasound waves. This helps to further break up the clot. This tool is portable and is estimated to cut the declotting procedure time by more than half, from 10 hours to four hours. So far, the tool has only been tested in synthetic blood vessels, and more study is needed to bring this treatment to patients.

NANOVACCINES WEAPONIZED TO BATTLE TUMORS

A new vaccine designed to stimulate a multi-pronged immune response can stimulate the immune system to specifically attack a tumor, while simultaneously inhibiting the suppression of the immune system, which often occurs in people with cancer. The researchers also developed a way to shrink the vaccine molecule so that it can more easily reach the parts of the immune system to activate it. Using colon cancer that had spread to the lungs as a test case for this approach, the nanovaccine successfully blocked lung tumor growth in a mouse model. Further testing revealed that mice receiving the nanovaccine had a significant increase in a type of immune cell that can target cancerous cells. Another potential benefit of this approach is that it mounts an anti-tumor immune response that circulates through the system, and therefore is particularly valuable for finding and inhibiting metastatic tumors growing throughout the body.

SOLVING A COMMON HEART DISEASE WITH ENGINEERING

Ischemic cardiovascular disease is a result of impaired blood circulation to tissues and organs and is the leading cause of death and disability in the U.S. Damage to small blood vessels is difficult to treat and can result in heart failure, stroke, or other arterial diseases. To address this problem, researchers developed a way to grow new blood vessels using 3D printed patches. The specially designed patches are seeded with cells and implanted into damaged areas. Once implanted, the patches induced the growth of new blood vessels. This early stage, basic research is an example of interdisciplinary teams including engineers, biologists, and clinicians combining their expertise and collaborating to solve health problems.

ADVANCES FROM NIBIB LABORATORIES

While the majority of NIBIB's budget supports research projects throughout the U.S., NIBIB also supports a small, but robust program within its Intramural Research Program (IRP).

These investigators are working to create optical imaging technologies that provide unprecedented high resolution and speed to study living cells in real time. Others create “theranostic” imaging probes—based on nanomaterials—that combine therapeutic and diagnostic capabilities to improve early diagnosis, monitor therapeutic responses, and guide drug discovery and development.

In one example, researchers developed a new radiotracer to help diagnose prostate cancer. Prostate cancer is the fifth leading cause of death worldwide and is especially difficult to diagnose, particularly early on. While prostate cancer is relatively easy to treat in its initial stages, it is prone to metastasis and can quickly become deadly. The research team developed a radiotracer that could identify prostate cancer at all stages. This new tracer is one of the first dual-receptor target tracers, which target more than one biomarker, to be studied in humans. This new method improves on the current practice that can lead to many false positive results and cause the patient to undergo unnecessary treatments or painful biopsies. A successful Phase I clinical trial with a small group of patients to establish safety and identify any possible side effects was recently completed.

CONCLUSION

Advances in technology are catalyzing the development of solutions to previously intractable disorders and improved approaches to biomedical research. As these examples illustrate, this type of research requires many disciplines to work together. This integration of disciplines is what defines NIBIB’s approach. NIBIB is committed to supporting such teams of researchers to solve major biomedical challenges that will improve the health of all Americans.

Jill Heemskerk, Ph.D.
Acting Director
National Institute of Biomedical Imaging and Bioengineering

Jill Heemskerk, Ph.D., is Acting Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB). She has an 18-year record of distinguished service at the National Institutes of Health. She joined NIBIB in 2014 as Associate Director for Research Administration and was subsequently appointed NIBIB Deputy Director. She came to NIBIB from the National Institute of Mental Health, where she was Deputy Director for the Division of Adult Translational Research, focused on clinical trials in psychiatry. Before this, she was Acting Director of the Office of Translational Research at the National Institute of Neurological Disorders and Stroke. There, she built a large program in pre-clinical therapeutics development for neurological diseases, emphasizing drug discovery chemistry and translation of basic research findings to the clinic. She established a drug development program called the NIH Blueprint Neurotherapeutics Network, a ‘virtual pharma’ forum that continues to thrive as a model for academic collaboration with small businesses and the pharmaceutical industry.

Dr. Heemskerk has served on scientific advisory boards for the ALS Association, the Spinal Muscular Atrophy Foundation, and the Huntington’s Disease Society of America. She earned her Ph.D. in Biochemistry and Biophysics from the University of California at San Francisco and conducted research in developmental molecular genetics at Columbia University.

PREPARED STATEMENT OF DIANA W. BIANCHI, M.D.
DIRECTOR, *EUNICE KENNEDY SHRIVER*
NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH).

ACHIEVING LIFELONG HEALTH

Understanding human development, both normative and atypical, is at the core of NICHD's mission. As our name reflects, NICHD supports and conducts a wide range of research, including but not limited to pediatric research, on all phases of human development to maturity, with the goal of achieving optimal health, cognitive, and physical function.

Child Health – The epidemic of opioid use disorder and its consequences is among the most serious public health threats in this country today. Among those exposed to opioid use are the thousands of infants born to women with the disorder. Every 15 minutes, a baby is born with Neonatal Opioid Withdrawal Syndrome (NOWS) in the United States; to date, NOWS has cost about \$2 billion in additional costs for Medicaid-financed deliveries.⁸ Symptoms of NOWS, also known as Neonatal Abstinence Syndrome (NAS), often do not begin until after infants have been discharged from the hospital. Their needs are placing huge stresses on the health care and foster care systems nationwide. To address this problem, NIH launched a new study called the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) to evaluate treatment options and improve clinical care of affected infants. The study is a collaboration between NICHD's Neonatal Research Network and the new IDeA States Pediatric Clinical Trials Network (within the Office of the NIH Director's Environmental Influences on Child Health Outcomes program), with sites located in rural and medically underserved communities. This joint research effort will use the reach of both networks to assess the prevalence of NOWS, understand current approaches to managing these cases, and develop protocols for conducting large scale studies to inform clinical care, so that these babies may get a better start in life.

One of NICHD's longest standing research priorities is to improve the lives and health of people with intellectual and developmental disabilities, such as Down syndrome. NICHD leads the public-private Down Syndrome Consortium, which includes 11 NIH Institutes and Centers, 13 national and international organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members. Consortium members provided valuable input to *DS Directions: The NIH Down Syndrome Research Plan*. Among the plan's major objectives is the call for research on the co-existing conditions commonly experienced by people with Down syndrome. For example, studies show that virtually all middle-aged adults with Down syndrome exhibit the neuropathological hallmarks of Alzheimer's disease, 50 percent of whom will develop this type of change to the brain by age 40. Funded jointly by NICHD and the National Institute on Aging, a new project, the Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS), seeks to identify biomarkers and use brain imaging to help us understand

⁸ Winkelman, T.N., Villapiano, N., Kozhimannil, K.B., Davis, M.M., Patrick, S.W., Incidence & Costs of Neonatal Abstinence Syndrome among Infants with Medicaid: 2004-2014, *Pediatrics* published online: March 23, 2018 (doi: 10.1542/peds.2017-3520).

the progression of the disease. In addition, the research teams will make their data and samples freely available to qualified researchers worldwide, with the goal of accelerating the testing of potential interventions, which in turn may have widespread implications for Alzheimer's and other conditions. In FY 2018, NICHD will lead a major new initiative to explore the risk and resilience of people with Down syndrome to common, co-existing conditions such as autism, cancer, and cardiovascular disease.

NICHD's research on child health explores basic biological processes that control healthy or atypical development, translational research, behavioral and social science, and clinical studies. Basic research studies provide fundamental knowledge essential to understanding causes of structural and functional birth defects. NICHD has long provided the evidence base informing the panel of conditions included in newborn screening tests to help diagnose and treat infants early. Further, in collaboration with NHGRI, the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) is exploring the challenges and opportunities associated with sequencing the entire genome of a newborn infant to advance our understanding of undiagnosed disorders. And, although it is widely recognized that children are not small adults, only five of the 80 drugs most frequently used in newborns and infants have been labeled for pediatric use to date. However, progress is being made under The Best Pharmaceuticals for Children Act, reauthorized by Congress for the fourth time in summer 2017, which charged NIH/NICHD with leading a trans-NIH effort on pediatric therapeutic needs. This year, through its Pediatric Trials Network, NICHD tested a commonly used combined antibiotic (piperacillin-tazobactam), finding the dose of this combination drug that is safe for infants who acquire severe infections in the hospital. NICHD-supported researchers also recently reported that children who are engaged during shared reading experience a boost in the area of the brain that is involved in language development, comprehension, memory, and problem solving; understanding how reading shapes a child's brain can help educators and parents develop and use effective early learning strategies.

Maternal Health – The World Health Organization defines maternal mortality as the death of a woman while pregnant or within 42 days after the pregnancy ends due to causes related to or aggravated by the pregnancy. Between 1987 and 2013, maternal mortality in the United States increased from 7.2 to 17.3 per 100,000 live births, the only developed nation in which the rates have been rising since 2000. NICHD supports a wide range of research efforts to counter this disturbing trend. For example, NICHD-supported researchers studying placental abruption (a dangerous condition that occurs when the placenta separates from the uterus before birth) found that women who had a placental abruption were about twice as likely to have abnormal levels of specific proteins in their blood. These results may help identify women at risk in the future.

NICHD is supporting two major projects to gather unprecedented amounts of information about pregnancy. Its ongoing Human Placenta Project, designed to provide insights into placental health noninvasively and in real time, continues to yield new data to improve maternal health and pregnancy outcomes. Another effort launched this year, PregSource®, is a longitudinal, crowd-sourced, citizen science registry that will expand our knowledge about women's typical experiences during pregnancy and after birth, the effects of pregnancy on women's lives, and special health challenges some women face. In addition, many pregnant or breastfeeding women must either take prescription medications to ensure their own health or are urged to take medications to benefit the baby's health outcomes. As part of the 21st Century Cures Act

legislation, NICHD was asked to lead the newly mandated federal Task Force on Research Specific to Pregnant Women and Lactating Women. Although pregnant women in the United States take between three and five prescription medications, usually for serious health conditions, very few of these therapies have been tested during pregnancy. Almost nothing is known about the transfer of medications into breast milk, nor the risks and benefits of breastfeeding while on medication. The Task Force's report and recommendations are due to the Secretary of Health and Human Services and Congress by September 2018, which will shed light on this understudied issue.

Rehabilitation – About five percent of children aged 5 to 17 in the United States live with disability. Conditions such as brain injury, cerebral palsy, or spina bifida can impede children's education and future potential to lead productive lives. The 2016 NIH Research Plan on Rehabilitation, led by the National Center for Medical Rehabilitation Research (NCMRR) at NICHD and the trans-NIH Rehabilitation Working Group, set out priority areas for medical rehabilitation research and assistive technologies to improve the lives of people of all ages. Multiple funding opportunities have been published to encourage scientists to submit applications on topics such as sleep disorders during medical rehabilitation; grants recently have been awarded on the biomechanics of movement and regenerative medicine. Another priority is to support research that will improve function for individuals with limb loss, yet the lack of data on the number of individuals who experience limb loss and the types of procedures or devices they receive to enable them to return to optimal function at home, school and work, has presented a barrier to research in this area. This year, NCMRR, in partnership with the Department of Defense, will solicit applications for a nationwide Limb Loss Registry to enable researchers the data they need to develop new devices and track health and functional outcomes.

Helping young scientists – To continue to foster groundbreaking health research, NICHD's commitment to investing in the next generation of researchers has been unwavering. For example, the Institute holds an annual young investigators conference to facilitate the training of physician scientists. The conference focuses on developing the skills needed by young clinician investigators who are working in any of the areas within NICHD's mission. We are also analyzing long-term success as a function of different types of training awards so that training resources can be directed to provide the maximum return on investment. To help young investigators get started with testing hypotheses and performing original research and to make maximum use of public investment, NICHD makes data and other research resources available through the Data and Specimen Hub (DASH), which offers de-identified data from clinical research on pregnancy, infant care, child health, HIV/AIDS, and other topics. Currently, the repository includes data from 63 studies, and more than 12,000 users have visited the site, including many young investigators who are exploring possible research collaborations; future plans include linking hundreds of thousands of residual biospecimens to the de-identified data.

CONCLUSION

To capitalize on the many scientific areas within NICHD's mission, and to determine scientific priorities, the Institute is engaging in a new strategic planning process, with input from a wide array of stakeholders, and in collaboration with NIH and scientific leadership. As the new plan emerges, NICHD will continue its life-changing research efforts to improve the lives of children and families.

Diana W. Bianchi, M.D.
Director
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**

Diana W. Bianchi is the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health in Bethesda, Maryland. She is also an investigator in the National Human Genome Research Institute. Formerly, she was the Executive Director of the Mother Infant Research Institute at Tufts Medical Center and the Natalie V. Zucker Professor of Pediatrics, Obstetrics and Gynecology at Tufts University School of Medicine. She was also Vice Chair for Pediatric Research at the Floating Hospital for Children in Boston, Massachusetts.

Dr. Bianchi is a *magna cum laude* graduate of the University of Pennsylvania. She received her M.D. from Stanford University School of Medicine and her postgraduate training in Pediatrics, Medical Genetics, and Neonatal-Perinatal Medicine at Boston Children's Hospital and Harvard Medical School. She is board-certified in all three specialties. Her clinical expertise is in prenatal and neonatal genetics and genomics.

Dr. Bianchi's research focuses on noninvasive prenatal diagnosis to develop novel fetal therapies for genetic disorders such as Down syndrome. Dr. Bianchi has published over 300 peer-reviewed articles and is Editor-in-Chief of the International Society for Prenatal Diagnosis' (ISPD) official journal, [Prenatal Diagnosis](#).

Dr. Bianchi has held multiple leadership positions in professional societies, including President of the ISPD and the Perinatal Research Society, council membership in the Society for Pediatric Research and the American Pediatric Society, and as a Director in the American Society for Human Genetics. Dr. Bianchi has received multiple awards, including the Christopher Columbus Spirit of Discovery Award and the Distinguished Faculty Award, both from Tufts University, , the 2015 Neonatal Landmark Award from the American Academy of Pediatrics, the 2016 Maureen Andrew Award for Mentorship from the Society for Pediatric Research, the 2016 Massachusetts Society for Medical Research's annual award, the 2017 Colonel Harland Sanders Award for Lifetime Achievement in Medical Genetics from the March of Dimes, and the 2017 J. E. Wallace Sterling Lifetime Achievement Award from the Stanford University School of Medicine. In 2013 she was elected to the National Academy of Medicine, and she is a past member of NICHD's National Advisory Child Health and Human Development Council.

PREPARED STATEMENT OF DR. NORA VOLKOW, DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH).

DRUG USE AND ADDICTION RESEARCH PRIORITIES

As a part of NIH, the Nation's premier biomedical research agency, NIDA's mission is to advance the science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health. NIDA-supported research has transformed our understanding of how biological, social, and environmental factors contribute to substance use disorders (SUD), generating new knowledge that fosters the development of smarter means for preventing and treating SUDs.

Substance use and SUDs represent a constant and dynamic threat to the health and well-being of our Nation. Their combined toll is more than \$740 billion a year in healthcare, crime, and lost productivity; but dollars barely capture the devastating human cost of addiction to individuals, families, and communities. In 2016 alone, over 63,000 Americans died because of an unintentional drug overdose. Over 42,000 of these deaths are attributable to opioids, due in large part to the spread of powerful synthetic opioids such as fentanyl and its analogues. Other challenges include the disconcerting rise in fatalities associated with cocaine and methamphetamine use, as well as the rise of new synthetic drugs and delivery systems, such as e-cigarettes, that are changing how people perceive and use drugs.

Despite these complex challenges, this is a time of great opportunities. In the last few years we have seen huge technological advances and new research applications, from deep sequencing to precise gene editing tools, and from more powerful brain imaging technologies to mobile health platforms and electronic health records.

NIDA's commitment to leveraging these advances through synergistic collaborations with federal, community, and industry partners has been codified in the 2016-2020 Strategic Plan, which charts our path forward according to four broadly defined goals designed to:

- Understand the complex multilevel interactions influencing drug use trajectories.
- Accelerate the development of treatments for SUDs.
- Address real-world complexities including comorbidities and poly-drug use.
- Advance bi-directional translation from basic to clinical and applied research.

RESEARCH HIGHLIGHTS

I'd like to highlight several high priority research areas that NIDA is pursuing, the most prominent of which is addressing the opioid crisis with medications development and implementation research efforts as well as assessing the impact of adolescent drug use on brain development and behavior that will build the evidence for personalized prevention.

OPIOID CRISIS

Millions of Americans are suffering from an opioid use disorder (OUD). The urgency and scale of this crisis calls for innovative solutions:

Medications development. The Division of Therapeutics and Medical Consequences supports synthesis and preclinical evaluation of potential therapeutics, clinical trial design and execution, and preparing regulatory submissions of medications. While there are current treatments available to reverse opioid overdose and treat opioid use disorder, the continued epidemic underscores the need for improved treatment options. In addition to current projects, new projects on reformulating drugs are underway and supported by NIDA grants and contracts. For example, NIDA support is accelerating the development of extended release formulations of existing medications used to treat OUD (methadone, buprenorphine, and naltrexone), as well as new medications to prevent and reverse overdoses from synthetic opioids or from drug combination (alcohol and heroin).

Criminal Justice. Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS) is guided by the philosophy that all juvenile offenders can benefit from evidence-based drug use and HIV-related prevention, screening, and treatment interventions. JJ-TRIALS builds on the strong foundation of our past work with criminal justice populations and includes three interrelated research efforts: (1) a national survey of existing practices within the juvenile justice system, (2) a large-scale, multi-site randomized study of data-driven strategies to improve justice systems' capacity to identify unmet substance use service needs, and (3) a pilot study examining the capacity to form partnerships with public health providers to address HIV and sexually transmitted infection risk behaviors.

Rural communities. In rural areas, a lack of treatment infrastructure and poor access to care hamper efforts to stem the tide of opioid addiction. Together with SAMHSA, CDC, and the Appalachian Regional Commission (ARC), NIDA is funding research to reduce the adverse outcomes of injection opioid use in rural communities. Initial projects focused on epidemiology, infrastructure, and policy issues to lay foundation for future research and planning efforts throughout Appalachia, while subsequent projects are testing the effectiveness of community response models and best practices in responding to opioid injection epidemics that can be implemented in similar rural communities across the US.

Developing alternative pain treatments with reduced abuse potential. In addition to these strategies to reverse the opioid overdose epidemic, we must develop more effective and less addictive treatments for chronic pain; NIDA is working with the NIH Pain Consortium to promote research in this key area. Funded grants span the entire range of the therapeutics development spectrum from preclinical safety and efficacy testing and early phase human trials, to health services research. Worth highlighting in this context are new molecular imaging technologies like x-ray crystallography that revealed the molecular structure of the receptors that mediate drugs' effects, information that is already leading to the development of safer medications to treat pain including the potential for developing an opioid pain medication devoid of addictive effects.

ADOLESCENT DRUG USE AND BRAIN DEVELOPMENT

A deeper understanding of how biological, environmental, social, and developmental factors interact and contribute to SUD risk is critical for developing better prevention and treatment strategies. This is particularly true when trying to understand how early onset drug use impacts developmental processes. To address this high priority need, NIDA has launched, jointly with other NIH institutes, centers, and offices the Adolescent Brain and Cognitive Development (ABCD) study, the largest long-term study of brain development and child health in the United States. Approximately 10,000 children ages 9-10 will be studied at 21 research centers across the country; they will be followed into early adulthood with brain-imaging, genetic, neuropsychological, behavioral, and other health assessments. The results will expand our understanding of how drugs can disrupt a young person's life trajectory. As of March 2018, more than 8,300 participants were enrolled in the study and close to 30 terabytes of data—about three times the size of the Library of Congress collection—had been obtained from the first 4,500 participants.

PREVENTION AND TREATMENT

Substance use disorders present a fascinating phenomenon: they are wholly preventable but when they strike, they can be utterly catastrophic. Hence, it is important to reassess our stance *vis á vis* prevention and treatment as often as possible and in response to new developments including the need for prevention strategies to protect against opioid initiation that is rising among young adults (early twenties).

Prevention and Treatment. NIDA supports integrated approaches to understanding and developing strategies to addressing the interactions between individuals and environments that contribute to substance use by fielding the annual Monitoring the Future survey of adolescent students. NIDA also supports the National Drug Early Warning System (NDEWS) network to survey emerging trends related to illicit drug use. The Division also supports research on integrating prevention and treatment services into healthcare and community systems to reduce the burden of drug problems across the lifespan. Ongoing research is exploring SUD treatment in the criminal justice system, including studies on implementation of medication-assisted treatment (MAT) and seek, test, treat, and retain (STTR) strategies for people with SUDs who are also at risk for HIV. NIDA also funds research into the efficacy of screening, brief intervention, and referral to treatment (SBIRT) in primary care settings for reducing drug use including opioid use disorders. Our research also examines the implementation of evidence-based universal as well as tailored prevention interventions and treatment services in real-world settings. For instance, NIDA is funding researchers to partner with states as they use the State Targeted Response funding from the 21st Century Cures Act to test approaches for expanding access to MAT for opioid use disorder and naloxone for the reversal of opioid overdoses.

The NIDA Clinical Trials Network (CTN) is a collaborative partnership with clinicians, researchers, and participating patients that cooperatively develops, tests, and delivers new treatment options to patients with SUD including opioid addiction. The CTN studies behavioral, pharmacological, and integrated treatment interventions in rigorous, multisite clinical trials across a network of community-based treatment settings. Current CTN-funded trials include

studies on how to implement buprenorphine in emergency departments and by primary care physicians, engagement of pharmacists for prescribing and monitoring buprenorphine to patients with an OUD and the effectiveness of a combination pharmacotherapy regimen to treat methamphetamine use disorder, among others.

Our efforts to develop effective addiction treatments respond to urgent needs while facing significant challenges. For example, despite remarkable advances in recent years, our menu of effective addiction treatments still presents critical gaps. Most notably, there continues to be a dire need for therapies to help treat addiction to stimulant drugs, like cocaine and methamphetamines or to help treat addiction to marijuana. As a result, NIDA is committed to evaluating the potential of emerging new therapies for SUDs, including pharmacological and non-pharmacological (e.g. psychosocial, biofeedback, brain stimulation technologies). For example, NIDA's IRP is collaborating with partners in the pharmaceutical industry to study a potential medication to decrease methamphetamine craving and collaborating with Italian researchers to test the efficacy of transcranial Magnetic Stimulation (TMS) for treatment of cocaine use disorders. The IRP is also exploring interventions to reverse the impact of prefrontal cortex deficits caused by cocaine or heroin use and to develop clinically useful indicators (biomarkers) of addiction severity or treatment efficacy that will support the development of more effective treatments.

CONCLUSION

Substance use and its attending disorders are complex conditions. The FY 2019 budget request will allow NIDA to support cutting-edge research that leverages the most powerful technologies and latest emerging opportunities to expand our understanding of drug use and addiction in order to enhance prevention and treatment, help address public health emergencies, and improve the health of the public.

Biography of Dr. Nora Volkow

Nora D. Volkow, M.D., became Director of the National Institute on Drug Abuse (NIDA) at the National Institutes of Health in May 2003. Dr. Volkow's work has been instrumental in demonstrating that drug addiction is a disease of the human brain. As a research psychiatrist and scientist, Dr. Volkow pioneered the use of brain imaging to investigate addiction. Her studies have documented addiction-related changes in the dopamine system affecting, among others, the functions of frontal brain regions involved with motivation, drive, and pleasure. She has also made important contributions to the neurobiology of obesity, ADHD, and aging.

Dr. Volkow was born in Mexico, attended the Modern American School, and earned her medical degree from the National University of Mexico in Mexico City, where she received the *Robins* award for best medical student of her generation. Her psychiatric residency was at New York University, where she earned the *Laughlin Fellowship Award* as one of the 10 Outstanding Psychiatric Residents in the USA.

Dr. Volkow spent most of her professional career at the Department of Energy's Brookhaven National Laboratory (BNL) in Upton, New York, where she held several leadership positions including Director of Nuclear Medicine, Chairman of the Medical Department, and Associate Director for Life Sciences. In addition, Dr. Volkow was a Professor in the Department of Psychiatry and Associate Dean of the Medical School at the State University of New York (SUNY)-Stony Brook.

Dr. Volkow has published more than 715 peer-reviewed articles and written more than 100 book chapters and non-peer-reviewed manuscripts and has also edited four books on neuroimaging for mental and addictive disorders and co-edited an Encyclopedia on Neuroscience and Brain Disorders. During her professional career, Dr. Volkow has been the recipient of multiple awards. In 2013, she was a Samuel J. Heyman Service to America Medal (Sammies) finalist and was inducted into the Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) Hall of Fame. She was elected to membership in the National Academy of Medicine of the National Academy of Sciences, received the International Prize from the French Institute of Health and Medical Research for her pioneering work in brain imaging and addiction science, and was awarded the Carnegie Prize in Mind and Brain Sciences from Carnegie Mellon University. She has been named one of *Time* magazine's "Top 100 People Who Shape Our World", "One of the 20 People to Watch" by *Newsweek* magazine, *Washingtonian* magazine's "100 Most Powerful Women" in both 2015 and 2017, "Innovator of the Year" by *U.S. News & World Report*, and one of "34 Leaders Who Are Changing Health Care" by *Fortune* magazine. Dr. Volkow was the subject of a 2012 profile piece by CBS's 60 Minutes⁹ and was a featured speaker at TEDMED 2014.¹⁰

⁹ <http://www.cbsnews.com/news/hooked-why-bad-habits-are-hard-to-break/>

¹⁰ <http://www.tedmed.com/talks/show?id=309096>

**PREPARED STATEMENT OF DR. JAMES F. BATTEY, JR., M.D., PH.D.
DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER
COMMUNICATION DISORDERS**

Mr. Chairman and Members of the Subcommittee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health (NIH).

NIDCD conducts and supports research and research training in the normal and disordered processes of hearing, balance, taste, smell, voice, speech, and language. NIDCD focuses on disorders that affect the quality of life of millions of Americans in their homes, workplaces, and communities. The physical, emotional, and economic impact for individuals living with these disorders is tremendous. NIDCD continues to make investments to improve our understanding of the underlying causes of communication disorders, as well as their treatment and prevention. It is a time of extraordinary promise, and I am excited to be able to share with you some of NIDCD's ongoing research and planned activities on communication disorders.

PREVENTING HEARING LOSS CAUSED BY COMMON CANCER DRUG

NIDCD intramural researchers have discovered why cisplatin and other popular and effective platinum-based chemotherapy drugs cause ototoxicity — damage to the delicate cells in the inner ear which can lead to hearing loss. In previous studies, researchers have focused on why the inner ear is more vulnerable to cisplatin ototoxicity than other areas in the body. The NIDCD research team, however, studied the cause of cisplatin ototoxicity from a different perspective; they explored if cisplatin remains in the inner ear continuing to cause damage for a longer time than in other areas of the body. The scientists found that, both in mice and humans, cisplatin remains in the inner ear long after it is already eliminated from other areas of the body. These results suggest that the inner ear readily takes up cisplatin, but it has little ability to remove the drug.

In mouse and human tissues, the research team saw the highest accumulation of cisplatin was in a part of the inner ear called the stria vascularis, which is responsible for maintaining the positive electrical charge in inner ear fluid that certain cells need to detect sound. The research team determined that the accumulation of cisplatin in the stria vascularis portion of the inner ear contributed to cisplatin-related hearing loss.

This research suggests that if we can find ways to avoid cisplatin from entering the stria vascularis during treatment with cisplatin, we might be able to prevent the hearing loss that goes along with it. As hearing loss is often associated with isolation, depression, and other conditions, helping to preserve hearing in individuals who are required to undergo cancer treatment with these chemotherapy drugs would greatly contribute to maintaining the quality of their lives.

TREATING HEREDITARY DEAFNESS WITH GENE EDITING

Hearing problems in infants and children can delay the development of voice, speech, and language skills. Approximately 80 percent of hearing loss is due to genetic factors, and treatment options for genetic deafness are limited. A research team, supported in part by NIDCD, used a mouse model of human genetic deafness to design a potential treatment approach.

Mutations in a particular gene, TMC1, are known to cause hereditary deafness in both humans and mice. The mutation causes the death of sensory hair cells in the cochlea of the inner ear. These hair cells transform sound waves into electrical signals that the brain recognizes as sound. To prevent hair cell death and the resulting progressive hearing loss in mice with the TMC1 mutation, the scientists used the CRISPR-Cas9 gene-editing system to remove the mutation and disable the gene.

The researchers developed a novel approach to deliver the gene-editing complex into the inner ears of newborn mice. They packaged the gene-editing complexes in lipids (fats) that form structures called liposomes. The liposome-packaged complexes move readily through cell membranes into cells. Eight weeks later, substantially more hair cells survived in ears of treated compared to untreated mice. The treatment also significantly reduced progressive hearing loss. This novel strategy may help scientists develop new therapies for hearing loss caused by inherited genetic mutations.

TASTE, BALANCE, AND MORE – A PROTON CHANNEL WITH MANY ROLES

Our ability to taste helps us choose and enjoy nutritious foods and avoid foods that have been spoiled by bacteria. On our tongue, sensory taste cells respond to chemicals that are released from food and drink. Taste cells respond to these chemicals via protein receptors and channels that are specific to certain taste molecules. For instance, to detect sourness in food, specialized channels let protons (Hydrogen atoms) that are released from acidic sour-tasting foods enter proton-sensitive, “sour” taste cells on the tongue.

The identity of this “sour detector” protein has been elusive. Now, NIDCD-supported scientists have located a protein called OTOPI and determined that it forms a channel that allows protons to enter taste cells on the tongue. They have also confirmed that human OTOPI forms a channel with properties similar to those of the mouse OTOPI protein. When OTOPI gene was altered in mice, the scientists observed that taste cells had significantly fewer protons going into them. This evidence, together with other supporting studies on OTOPI, suggests that OTOPI is the long-sought after sour taste receptor. The next step to test this theory will be to record whether mice that lack OTOPI respond to sour tastes. Studies like this one, that increase our understanding about how we taste, may help scientists learn to restore a sense of taste to those who have lost it due to disease or injury.

This study may help us understand far more than just how we detect taste. OTOPI is also required for the vestibular (balance) system in the inner ear to detect gravity, so it is important for helping us keep our balance. OTOPI is also expressed in many other body tissues, including fat, heart, uterus, breast, and the nervous system. Since we know that OTOPI functions as a proton-sensitive channel, what we learn from this taste study may help us understand cell signaling in these other tissues, too. When protons enter cells, they change the acid/base (pH) concentration. So, a better understanding of OTOPI could also help us understand other body processes that involve changes in pH, such as pain sensation, fat metabolism, and pH changes seen in cancer cells.

PERSONALIZED VOICES FOR PEOPLE WITH SEVERELY IMPAIRED SPEECH

Approximately 2.5 million Americans and millions more people worldwide have a severe speech impairment since birth or as a result of a neurological disorder that occurred later in life, such as a stroke. For these people, communicating is a daily challenge that relies upon their use of a computer to generate their voice. While these devices go a long way toward helping people with a voice disorder express themselves, the synthetic voices produced are usually a poor

representation of a natural human voice. In addition, the lack of diversity in available synthetic voices means that many people must use the same generic voice.

Through a Small Business Innovation Research Program grant, NIDCD voice scientists have moved research from the lab into real-world application. Researchers are in the second phase of developing a personalized text-to-speech augmentative and alternative communication (AAC) device called VocaliD. This device involves blending the speech of two individuals — a donor and the recipient. First, a recording is made of whatever vocal sounds the recipient is still able to make. The next step is accomplished with the help of a volunteer voice donor. For the best results, the donor should match the recipient in terms of gender, age, region of origin, and other characteristics. By commercializing VocaliD, NIDCD scientists have refined the technology, automating certain steps and making the entire process of creating personalized, synthetic voices faster and more efficient. These improvements will advance speech synthesis while humanizing machine-mediated spoken interaction for AAC devices and beyond.

James F. Battey, Jr., M.D., Ph.D.

Director, National Institute on Deafness and Other Communication Disorders

James F. Battey, Jr., received his Bachelor of Science degree in physics from the California Institute of Technology in 1974. He received an M.D. and Ph.D. in biophysics from Stanford University School of Medicine in 1980. After receiving training in pediatrics, he pursued a postdoctoral fellowship in genetics at Harvard Medical School under the mentorship of Dr. Philip Leder. Since completing his postdoctoral fellowship in 1983, he has held a variety of positions at the National Institutes of Health, serving in the National Cancer Institute, National Institute of Neurological Disorders and Stroke, and the National Institute on Deafness and Other Communication Disorders (NIDCD). He is married to Frances Battey, and has two sons, Michael and JJ.

**PREPARED STATEMENT OF MARTHA J. SOMERMAN, DDS, PhD,
DIRECTOR, NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL
RESEARCH**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH).

The mission of NIDCR is to improve dental, oral, and craniofacial health through research, research training, and the dissemination of health information. A recent study looking at personal healthcare spending in the United States by condition estimates that Americans spend \$66.4 billion annually on the treatment of oral disorders and another \$48.7 billion for general dental care and preventive services. Together, the total surpasses the costs of treatment related to a common condition among Americans – diabetes – by more than \$13 billion¹¹. NIDCR leads the effort to reduce this burden by supporting basic, translational, and clinical research and research training to improve dental, oral, and craniofacial health. By promoting the timely translation of those findings into practice NIDCR helps advance treatment and prevention strategies for all Americans.

To prioritize emerging areas of scientific inquiry that are ripe for significant advances over the next decade, we launched a long-term strategic initiative called NIDCR 2030. As part of this bold, forward-looking plan, NIDCR will support research that integrates oral health into overall health and uncovers the common risk factors and underlying biological mechanisms of health and disease throughout the body. This knowledge will inform the development of new preventative and therapeutic interventions to improve dental, oral, and craniofacial health – as well as the health of the whole body.

PIONEERING A GENE THERAPY TO TREAT CHRONIC DRY MOUTH

For most people who survive head and neck cancers, successful treatment with radiation therapy comes at a high price – significant loss of salivary gland function, leading to chronic dry mouth and its adverse health effects. Radiation therapy works by killing malignant tumor cells, but it does not discriminate among cell types. It also kills saliva-producing cells, which causes saliva production to shut down. This can lead to problems chewing, tasting, talking, and swallowing food, and significantly increases the risks for dental decay, tooth loss, and oral infections. NIDCR supports research to unravel the complex molecular and cellular processes involved in salivary gland function and fluid secretion. These investments have inspired the development of a gene therapy to treat chronic dry mouth caused by radiation treatment. The therapy delivers specific DNA sequences into the surviving salivary gland cells, resulting in the production of specialized tube-shaped proteins called aquaporins, which allow water to flow out of the salivary gland cells. Studies in mouse models showed that the gene therapy generated enough aquaporin proteins to restore salivary flow. This research led to a clinical trial conducted on the NIH campus that is currently recruiting patients to test the gene therapy treatment in people whose salivary glands have been damaged by radiation therapy for head and neck cancer.

¹¹[Dieleman J. US Spending on Personal Health Care and Public Health, 1996-2013. JAMA. 2016; 316\(24\):2627-2646.](#)

Results from the first phase of the study are encouraging and suggest that this approach could be a promising treatment. Building on these studies, another clinical trial is being planned to see if the therapy can also be used to restore salivary function in individuals whose chronic dry mouth is caused by Sjögren's syndrome, an autoimmune disorder that damages salivary glands.

DEVELOPING INNOVATIVE TECHNIQUES TO ADVANCE REGENERATIVE MEDICINE

A major priority for NIDCR is advancing regenerative medicine research to improve the lives of those with dental, oral, and craniofacial conditions or diseases. A significant challenge in regenerating load-bearing tissues such as joint cartilage is engineering and growing tissues that are as strong and flexible as the body's natural ones. The cartilage that makes up joints, such as the temporomandibular joint in the jaw, must be extremely resilient to withstand a lifetime of repetitive movement and mechanical stress. To overcome this obstacle, NIDCR-supported scientists are developing techniques to generate functional tissues in the laboratory for regenerative medicine therapies. These scientists developed a device that physically pulls on single layers of cartilage cells while they are being grown on a flat, supportive matrix, resulting in tissues with strength and elasticity that more closely resembles natural cartilage. Using this technique results in engineered cartilage that is more resilient to wear and tear, making it especially useful as a potential replacement for damaged cartilage in highly mobile joints. Future uses could include the development of better treatment options for temporomandibular joint and muscle disorders (TMD) and joints damaged by osteoarthritis. Further development of this novel cartilage growth technique, and its expansion to other cell types could open the door to exciting possibilities for the engineering and generation of more durable and flexible tissues for use throughout the body.

FINDING PAIN RELIEF IN UNEXPECTED PLACES

Chronic pain is a major health problem that affects almost one-quarter of the US population¹². Opioids are often prescribed to alleviate chronic pain, although they carry a strong risk for addiction. Identifying new effective and non-addictive pain treatments remains a priority for NIDCR, especially in regard to TMD, a group of conditions that can cause severe and chronic pain in the jaw and muscles of the head and neck. In 2005, NIDCR launched OPPERA (Orofacial Pain, Prospective Evaluation and Risk Assessment) – a multi-site population-based study – to identify the biopsychosocial and genetic risk factors that cause TMD. Early OPPERA studies found an association between the gene for epidermal growth factor (EGFR) and the development of chronic pain in patients with TMD. Drugs that block the activity of EGFR are currently being used to inhibit tumor growth in some types of cancer. Strikingly, there have been case reports of cancer patients reporting a significant reduction in pain when treated with EGFR-blocking drugs. Taking these observations into the laboratory, NIDCR-funded investigators used a mouse model to show that EGFR-blocking drugs alleviate inflammatory and neuropathic pain. These drugs function by blocking the activity of EGFR in neurons that receive and interpret

¹²[Gereau RW, et al. A pain research agenda for the 21st century. J Pain. 2014; 15\(12\):1203–1214.](#)

sensory stimuli – such as pain – in the body. This intriguing finding could lead to the development of more effective treatments for chronic pain that also reduce the risks for addiction.

ADVANCING TREATMENTS FOR HPV-POSITIVE AND HPV-NEGATIVE OROPHARYNGEAL CANCERS

Oropharyngeal cancers form in the middle part of the throat, including the back of the mouth, base of the tongue, and the tonsils, and are often caused by HPV (human papilloma virus), the same virus that causes cervical cancer. These cancers are known as HPV-positive (HPV+) oropharyngeal cancers. Experts estimate that 60 to 70 percent of newly diagnosed oropharyngeal cancers in the United States are likely to be HPV+, especially among young men and women. Although people exposed to the HPV virus are more likely to develop oropharyngeal cancer, paradoxically, HPV+ cancers respond much more successfully to chemotherapy than HPV-negative (HPV-) cancers. A collaboration of clinicians and basic science researchers funded by NIDCR are studying the biomolecular reasons for this difference in treatment outcomes to see if there is a way to separate out the HPV+ beneficial response to treatment and then apply it to HPV-negative (HPV-) oropharyngeal cancers. To do this they looked closely at the activities of cisplatin – the most commonly used chemotherapy for many cancers – which is better at killing HPV+ cancer cells than HPV- cancer cells. The team discovered an HPV protein called E7 that enhances the effectiveness of cisplatin treatment, and then developed a small protein fragment (peptide) called E2F5 that mimics the HPV protein E7 without the HPV infection. Combining this novel peptide with cisplatin treatment in HPV-negative patients led to improved outcomes, similar to those of HPV+ patients. Next steps will be to clear the FDA requirements for producing the E2F5 peptide and establishing treatment protocols for clinical trials.

Martha J. Somerman, D.D.S., Ph.D.
Director, National Institute of Dental and Craniofacial Research

Dr. Martha J. Somerman is the director of the National Institute of Dental and Craniofacial Research (NIDCR), a position she has held since August 2011. Also, she is chief of the Laboratory for Oral Connective Tissue Biology, National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Prior to becoming NIDCR director, Dr. Somerman was the dean of the University of Washington School of Dentistry and professor in Periodontics (2002-2011). She served as associate dean for research (2001-2002) and chair of the Department of Periodontics/Prevention and Geriatrics (1995-2000) at the University of Michigan School of Dentistry and was a professor of Pharmacology at the School of Medicine (1995-2002). From 1984 to 1991, she served on the faculty of the University of Maryland School of Dentistry in the departments of Periodontics and Pharmacology. In the early 1980s, she was a staff fellow at the National Institute of Dental Research (now NIDCR), serving first in the Developmental Biology and Anomalies Laboratory and then in the Laboratory of the Clinical Investigations and Patient Care Branch. Dr. Somerman earned her B.A. in biology from New York University (NYU) in 1968 and her D.D.S. degree from NYU in 1975, a certificate in periodontology (1978) and PhD in pharmacology (1980) from the Eastman Dental Center and University of Rochester.

Dr. Somerman's research focuses on defining key regulators controlling development and regeneration of tissues that form the dental-oral-craniofacial complex and applying the knowledge gained to design therapies to regenerate tissues lost as a consequence of periodontal diseases and conditions. She has published more than 170 peer-reviewed articles and made important contributions to the periodontal research field. Prior to joining NIDCR, Dr. Somerman served on several editorial boards, reviewed grants submitted to NIH/NIDCR and the National Center for Research Resources (NCRR), and served on committees for the American Association for the Advancement of Science (AAAS), the IADR/AADR (International/American Association for Dental Research) and American Dental Association. In addition, she served on the Government Advisory Committee of the AADR, advising on public policy in the areas of dental and biomedical research, education and training, access and disparities in care, and research infrastructure and workforce.

Dr. Somerman's awards and honors include IADR's Distinguished Scientist Award for Basic Research in Biological Mineralization (2018) and for Research in Oral Biology (2005). Dr. Somerman received the Distinguished Scientist Award (2016) and the Geis Award (2003) from the American Academy of Periodontology; delivered the John T. Hamilton Distinguished Lectureship at Western University in Canada (2014); received the NYU College of Dentistry Distinguished Scientist Award (2012); received the IADR /Straumann Award in Regenerative Periodontal Medicine (2010); and received the Paul Goldhaber Award from the Harvard School of Dental Medicine (2011). She was named a diplomate of the American Board of Periodontology in 1990 and served as president of AADR in 2001. In addition, Dr. Somerman is a fellow of AAAS, the International College of Dentists, and the American College of Dentists.

**PREPARED STATEMENT OF GRIFFIN P. RODGERS, M.D., M.A.C.P.
DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY
DISEASES**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH).

COMBATING CHRONIC DISEASE TO IMPROVE HUMAN HEALTH

NIDDK supports research on diseases and conditions affecting the health and well-being of millions of Americans. Its mission spans diabetes and other endocrine and metabolic diseases; digestive and liver diseases; kidney and urologic diseases; blood diseases; obesity; and nutrition disorders. Though diverse in nature, most of these diseases and conditions are chronic, consequential, and costly. For example, diabetes, kidney disease, and digestive diseases alone run into hundreds of billions of dollars yearly for medical care, disability, loss of work or productivity, and other costs. Obesity is at high prevalence among U.S. adults and youth and is a risk factor for many of these chronic and sometimes deadly health problems. The challenges are vast, and the needs urgent. Through research and related activities, NIDDK continues to seek out ways to prevent, treat, and cure chronic diseases and conditions to improve human health and quality of life.

RESEARCH

To foster discovery important to combating chronic disease, NIDDK supports a multi-faceted scientific portfolio spanning basic to translational to clinical studies, while also creating and leveraging partnerships that can fortify and accelerate research. For example, in basic research, scientists have used a specialized microscopy technique to develop a three-dimensional picture of a cellular protein that is a target for certain diabetes drugs. Because this protein is also a member of a protein "family" targeted by about 40 percent of pharmaceutical drugs on the market today, the intricate knowledge gained from this work is not only important for diabetes but will inform the search for new drug treatments and refinement of current ones for other diseases. New findings in mice may also open up new therapeutic avenues important to prevention of obesity and type 2 diabetes: One research group has identified a group of brain cells that, upon activation, induces rapid binge eating and weight gain, while another has found that bones secrete a hormone that both suppresses appetite and regulates blood sugar levels. Studies in mice have also revealed a more complex view of the kidney's role in salt and water balance and blood pressure regulation and suggest new areas of investigation for human hypertension. NIDDK-supported scientists have also been able to produce human intestinal "organoids"—small bundles of cells that model various aspects of the small intestine and its functioning, facilitating study of certain digestive system diseases and disorders and creating potential for tissue replacement therapy.

In FY 2019, NIDDK will build upon research accomplishments such as these and upon other research avenues and continue its support for basic studies of both normal and disrupted biological functions and systems. For example, the ReBuilding a Kidney (RBK) consortium will

continue efforts to enable tissue repair or replacement in kidney disease; already, RBK scientists have found that selecting the proper substrate for growth and structural support is critical to creating blood supply in a “kidney on a chip.” Recent studies have shed light on the multiple levels of complex interactions that contribute to how human gut microbes affect health, from molecules produced by the microbes themselves to differences in human diet; a 2017 workshop on best practices for studies of diet and gut microbiome will help inform rigor and reproducibility in future efforts in this aspect of research on the gut microbiome, which is rapidly emerging as an important contributor to digestive diseases, obesity, nutrition, and many other chronic diseases and conditions.

Similarly, NIDDK-supported translational and clinical studies have yielded fruit. For example, in the translation of genetic discovery to treatment, NIDDK-supported scientists developed a personalized treatment plan for a child suffering from a severe anemia after discovering that the cause was a rare mutation affecting a protein already available in a therapeutic form. New findings about the impact of being diagnosed with diabetes before age 20 include that youth with type 2 diabetes are more than twice as likely as peers with type 1 diabetes to have or be at high risk of a diabetes health complication by age 21. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network has yielded important new insights into the nature and course of the urologic chronic pelvic pain syndromes interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), such as new knowledge about the prediction of and bodily patterns of pain. NIDDK-supported scientists have also developed the first method for calculating the average rate of blood filtration by the individual functional units in the human kidney, an important measure of kidney health. Discoveries such as these can now be harnessed into new research toward interventions or into other actions to improve health.

NIDDK will continue its support of research that, in partnership with human volunteers, can elucidate causes of and treatments and cures for chronic diseases and conditions and ways to implement those findings. For example, the third phase of the Diabetes Prevention Program Outcomes Study, spearheaded by NIDDK with several NIH partners, will study outcomes that are of increasing concern in an aging population with a high burden of pre-diabetes and diabetes. These include evaluating the potential benefit of the diabetes drug metformin on the development of cardiovascular disease and cancer. Gestational diabetes has long-term health impacts for affected mothers and children, and NIDDK will continue to capitalize on new findings and efforts to better understand this condition and identify ways to improve outcomes. Efforts will continue in development and testing of artificial pancreas systems for treatment of type 1 diabetes. NIDDK will also continue support for many clinical research efforts to address overweight and obesity, including major ongoing studies to assess the health risks and benefits of weight-loss surgery in extremely obese adolescents. The new Kidney Precision Medicine Project will pursue innovative efforts to elucidate the heterogeneity of kidney disease in human study participants, which could lead to novel and tailored treatments for both acute and chronic kidney disease. NIDDK will sustain its long-term investment in the Drug-Induced Liver Injury Network (DILIN) so that it may continue its highly productive and informative efforts to characterize liver injury from herbal and dietary supplements and prescription and over the counter drugs.

To help tackle complex challenges and move discovery forward, NIDDK continues to forge effective partnerships with other NIH ICs and Offices, other federal agencies, and private organizations. For example, the NIH Nutrition Research Task Force chaired by NIDDK and co-chaired by the National Heart, Lung, and Blood Institute (NHLBI), National Cancer Institute (NCI), and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has sought input from across NIH and external stakeholders and is developing the first NIH-wide strategic plan on nutrition. The public-private Accelerating Medicines Partnership-Type 2 Diabetes (AMP-T2D) project, spearheaded by NIDDK with partners from industry and nonprofit organizations, continues to exceed expectations in terms of progress and will continue augmenting content and access to genetic and clinical data on diabetes and related traits made available through its Knowledge Portal.

OTHER

Indivisible from research are the minds and hands that generate new ideas and bring forth results. NIDDK will continue to foster and grow a diverse biomedical research workforce that can meet, with innovation and creativity, the challenges posed by chronic diseases and conditions. NIDDK supports several special training opportunities spanning high school to medical school to attract students, including those underrepresented in science and medicine, to NIDDK research areas. Mentorship opportunities offered by NIDDK's Network of Minority Health Research Investigators, which celebrated its 15th anniversary in 2017, focus on junior investigators and will continue to promote a diverse research pipeline. NIDDK will also continue efforts to help the new generation of biomedical researchers realize their potential, such as priority funding strategies for those early in their careers. NIDDK is also pursuing multiple efforts to enhance rigor and reproducibility in research. Simultaneously, NIDDK will continue disseminating health and scientific information through multiple venues to educate and inform the public, healthcare providers, and researchers about new developments germane to chronic diseases and conditions.

CONCLUSION

In closing, NIDDK has a robust and vigorous commitment to research and related activities to combat chronic diseases and conditions. This is reflected in its five guiding principles: maintain a vigorous investigator-initiated research portfolio, support pivotal clinical studies and trials, preserve a stable pool of new investigators, foster research training and mentoring, and disseminate science-based knowledge through education and outreach programs. Through research, NIDDK hopes to advance progress toward new and improved prevention, treatment, and curative strategies.

Griffin P. Rodgers, M.D., M.A.C.P.
Director, National Institute of Diabetes and Digestive and Kidney Diseases

Dr. Griffin P. Rodgers was named director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health (NIH) on April 1, 2007. Dr. Rodgers served as the NIDDK's acting director March 2006 - April 2007 and was the Institute's deputy director from 2001 - 2007. Since 1998, Dr. Rodgers also serves as chief of the Molecular and Clinical Hematology Branch. The branch is now administratively managed by the NIH's National Heart, Lung, and Blood Institute.

Dr. Rodgers received his undergraduate, graduate, and medical degrees from Brown University in Providence, RI. He performed his residency and chief residency in internal medicine at Barnes Hospital and the Washington University School of Medicine in St. Louis. His fellowship training in hematology/oncology was through a joint program of the NIH with George Washington University and the Washington Veterans Administration Medical Center. In addition to his medical and research training, Dr. Rodgers earned a master's degree in business administration, with a focus on the business of medicine, from Johns Hopkins University in 2005.

As a research investigator, Dr. Rodgers is widely recognized for his contributions to the development of the first effective, and now FDA-approved, therapy for sickle cell anemia. He was a principal investigator in clinical trials to develop therapy for patients with sickle cell disease (SCD). He also performed basic research that focused on understanding the molecular basis of how certain drugs induce gamma-globin gene expression. Recently, he and his collaborators have reported on a modified blood stem-cell transplant regimen that is highly effective in reversing SCD in adults and is associated with relatively low toxicity.

Dr. Rodgers has been honored for his research with numerous awards, among them the 1998 Richard and Hinda Rosenthal Foundation Award, the 2000 Arthur S. Flemming Award, the Legacy of Leadership Award in 2002, and a Mastership from the American College of Physicians in 2005. He was a 2015 finalist for The Samuel J. Heyman Service to America Medals (Sammies).

Dr. Rodgers has been an invited professor at medical schools and hospitals in France, Italy, China, Japan, and Korea. He has been honored with many named lectureships at American medical centers and as commencement speaker at many medical schools. He has published more than 200 original research articles, reviews, and book chapters; has edited four books and monographs; and holds three patents.

Dr. Rodgers served as governor to the American College of Physicians for the Department of Health and Human Services from 1994 - 1997. He is a member of the American Society of Hematology; the American Society of Clinical Investigation; the Association of American Physicians; the National Academy of Medicine of the National Academies of Sciences, Engineering, and Medicine; and the American Academy of Arts and Sciences. He served as chair of the Hematology Subspecialty Board and a member of the American Board of

Internal Medicine Board of Directors. In 2017, Dr. Rodgers was elected as a fellow to the American Association for the Advancement of Science.

**PREPARED STATEMENT OF LINDA S. BIRNBAUM, PH.D., D.A.B.T, A.T.S
DIRECTOR, NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Environmental Health Sciences of the National Institutes of Health (NIH).

TEAM SCIENCE FOR HEALTH SOLUTIONS

Human beings are faced with an increasingly complex environment in which we experience thousands of exposures—both healthy and hazardous—on any given day over the course of our lifetimes. Although advances in knowledge and technology enable individual scientists to delve deeper than ever into how such exposures may impact our health, the use of diverse, multidisciplinary teams of scientists to investigate complex problems offer the promise of accelerated discovery to prevent disease and improve health. A 2015 report by the National Research Council concluded that “Several strands of research and data suggest that team science can rapidly advance scientific and technological innovation by increasing research impact, novelty, productivity, and reach.” Such outcomes are directly in line with the imperatives of Optimize NIH and ReImagine HHS to increase efficiency, maximize talent, and accelerate innovation.

Team science, in the NIEHS context, is the collaborative effort of researchers from diverse scientific disciplines, often in partnership with communities that have relevant experience or perspectives, to solve public health problems that arise from environmental exposures. NIEHS continues to build on a long tradition of interdisciplinary approaches that engage a range of scientific and community stakeholders in creating the knowledge to inform public health decision making. I will describe some of the ways in which we implement team science approaches as we work to fulfill the mission of the NIEHS—to discover how the environment affects people in order to promote healthier lives.

CENTERS, CONSORTIA, AND COLLABORATIONS

NIEHS both conducts team science intramurally and supports team science through a variety of center, consortia, and interagency collaborations. We use the centers framework to capitalize on the diverse talent at universities and create a supportive environment for multidisciplinary science and community engagement. NIEHS-supported centers include those focusing on areas such as Environmental Health Sciences, Breast Cancer and the Environment, Environmental Health Disparities, Children's Environmental Health and Disease Prevention, and Oceans and Human Health. These centers provide a centralized hub to support research, training, and scientific exchange among investigators across disciplines and often in partnership with patient advocacy or other community organizations. Each center must also conduct research translation, provide information and education, and engage with interested patient groups and communities.

The centers are highly productive and last year generated numerous significant discoveries, including how omega-3 fatty acids contained in fish oil could be used to treat asthma patients; that dementia is linked to a certain genetic variation combined with exposure to air pollution, and an impaired sense of smell in such persons may serve as an early warning sign; that children with asthma may be more likely become obese later in childhood or adolescence; links between exposure to seasonal harmful algal blooms and elevated risk of amyotrophic

lateral sclerosis (ALS); and potentially safer alternatives to bisphenol A (BPA), to name just a few.

Consortia are another way that NIEHS supports team science that extends beyond a single institution to create a network of linked expertise to focus on a complex environmental health problem or set of related issues. NIEHS led the Gulf Long-term Followup (GuLF) Study and the five-year, \$25.2-million Deepwater Horizon Research Consortia, both of which partnered researchers with communities to investigate health effects stemming from the oil spill, including the long-term mental health impacts of the spill on coastal residents, especially women and children; the resilience of individuals and communities; and whether seafood in the Gulf was safe for human consumption. These research partnerships continue to yield new insights: a 2017 study linked a range of health problems in workers who were exposed to dispersants used to clean up the oil spill.

Research needs identified by the Deepwater Horizon consortia provided further momentum for the creation of the NIH Disaster Research Response (DR2) program, which comprises a national framework for research on the medical and public health aspects of disasters and public health emergencies. Led by the NIEHS and the National Library of Medicine, DR2 has rapidly grown into a federal interagency effort with broad engagement in the goal of understanding how to be prepared for disasters and how to limit any negative disaster-related health effects. Examples of such research include human health studies to assess effects of exposures on first responders, worker volunteers, and community members; characterizing chemical hazards in floodwaters and identifying post-flood molds; and assessing risks to vulnerable people such as those with asthma from wildfire pollution. DR2 tools and trainings were used last year to enable critical data collection and analysis, and inform response to the devastating Hurricanes Harvey, Irma, and Maria. In addition, NIEHS awarded time-sensitive research grants specifically aimed at hurricane response research.

NIEHS is leading the nation's coordinated science response to another type of environmental threat—the potential for serious human health impacts from exposure to PFAS, the collective name for per- and polyfluoroalkyl substances, chemicals widely used over the past 50 years in food packaging, lubricants, water-resistant coating, and fire-fighting foams, and other manufacturing. Although some have been phased out, these endocrine-disrupting chemicals continue to be found in drinking water supplies in multiple states, and NIEHS-funded research suggests links to health effects on immune and thyroid function, fetal growth and development, risk of cancer and obesity, and others. NIEHS helped to organize a recent meeting of 16 federal agencies that focused on exchanging information on PFAS exposure science, health science, and remediation and treatment of contaminated areas, and generated opportunities for collaborative research. The National Toxicology Program Laboratory Branch, one of the NIEHS research components of this interagency program, is also responding to public demand for more and faster information on the threat posed by PFAS through its Rapid Evaluation and Assessment of Chemical Toxicity (REACT) program. Outcomes of these collaborative efforts will help to target research and inform decision making by both government and communities.

Perhaps the most prominent environmental hazard demanding a team science approach from across a broad spectrum of disciplines is lead exposure. NIEHS-supported science established the knowledge base for lead's major health impacts. But although we understand the primary outcomes of lead poisoning, particularly neurodevelopmental damage in children, the need continues for research to make clear exactly how lead works in the body to cause damage so that successful interventions can be developed. An NIEHS-funded study using lead in baby

teeth as a marker of exposure found associations between lead levels just before and after birth with the risk for and severity of autism in later childhood. Another study of children whose mothers took multivitamins during pregnancy suggested they were 30% less likely to develop autism. The concerns are not just for children however; a recent study estimated that low-level lead exposure (<5 µg/dL blood) is responsible for more than 400,000 deaths each year in the United States, some 250,000 of which from cardiovascular disease in adults. Combined with the estimated half million children still exposed beyond the CDC reference level, the health, economic, and societal consequences of lead exposure remain great. NIEHS and our grantees are continuing to respond to this threat through research, training for workers involved in lead cleanup and remediation, and engaging with our federal partners on the President's Task Force on Environmental Health Risks and Safety Risks to Children to develop a Federal Lead Strategy.

CONNECTING THE DATA POINTS

No matter what the environmental health issue is, it has become increasingly clear that finding solutions demands a strong commitment to team science—data science, sharing, and integration offer the promise of incredible breakthroughs in preventing disease and promoting health, but require unprecedented levels of engagement, coordination, and standardization across a rapidly evolving scientific landscape. NIEHS has been working to foster data collaborations through support of training grants in the Big Data to Knowledge (BD2K) initiative, partnership with the NIH Data Commons, development of an NIEHS Data Commons, convening of National Academies workshops, establishment of an Office of Cyberinfrastructure, and prioritization of data science and integration goals across our developing Strategic Plan.

To conclude, environmental health problems present large, costly, and complex issues for our society that demand the focused attention of multidisciplinary teams of scientists. NIEHS will continue to provide the critical support and leadership necessary for such teams to succeed in discoveries that will prevent disease and promote the health of the American people.

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director, National Institute of Environmental Health Sciences

Dr. Linda S. Birnbaum is director of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, and the National Toxicology Program (NTP). A board-certified toxicologist, Dr. Birnbaum has served as a federal scientist for nearly 39 years. Prior to her appointment as NIEHS and NTP Director in 2009, she spent 19 years at the U.S. Environmental Protection Agency (EPA), where she directed the largest division focusing on environmental health research.

Dr. Birnbaum has received many awards and recognitions. In 2016, she was honored with the North Carolina Award in Science, the highest civilian award given by the state. She was elected to the Institute of Medicine of the National Academies, one of the highest honors in the fields of medicine and health. She is a Fellow of the Collegium Ramazzini, an international academy of experts in the field of occupational and environmental health. She received an honorary Doctor of Science from the University of Rochester and an Honorary Doctorate from Ben-Gurion University, Israel, as well as a Distinguished Alumna Award from the University of Illinois. She received the Surgeon General's Medallion in 2014. By recommendation of the EPA's external Science Advisory Board, she received 14 Scientific and Technological Achievement Awards for specific research publications.

Dr. Birnbaum is the former vice president of the International Union of Toxicology, the umbrella organization for toxicology societies in more than 50 countries, and the former president of the Society of Toxicology, the largest professional organization of toxicologists in the world. Dr. Birnbaum's own research focuses on the pharmacokinetic behavior of environmental chemicals, the mechanisms of action of toxicants including endocrine disruption, and the linking of real-world exposures to human health effects. She is the author of more than 800 peer-reviewed publications, book chapters, and reports. She is an adjunct professor in the Gillings School of Global Public Health, the Curriculum in Toxicology, and the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill, as well as in the Integrated Toxicology and Environmental Health Program at Duke University. A native of New Jersey, Dr. Birnbaum received her M.S. and Ph.D. in microbiology from the University of Illinois at Urbana-Champaign.

**PREPARED STATEMENT OF JON R. LORSCH, PH.D. DIRECTOR, NATIONAL
INSTITUTE OF GENERAL MEDICAL SCIENCES**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of General Medical Sciences (NIGMS), a component of the National Institutes of Health (NIH).

The NIGMS focuses on promoting and supporting fundamental or "basic" biomedical research that increases scientific knowledge about how living systems work, from individual molecules to cells, organs, whole organisms, and populations. The Institute's priority is to support investigator-initiated research, based on the principle that the best scientific ideas, directions, and approaches stem from scientists themselves. Thus, NIGMS aims to enable creative, innovative, and ambitious research conducted by individuals and teams of investigators to promote scientific discovery and medical advancement.

One indication of the success of the Institutes' strategy is the number of Nobel Prizes awarded to NIGMS grantees. Of the 153 Nobels given for NIH-funded research, over half - 87 - have been for work supported by NIGMS. This year, the Nobel Prizes in both chemistry and in physiology or medicine were awarded to multiple NIGMS grantees. The 2017 Nobel Prize in chemistry was awarded to a NIGMS grantee and two others for the development of cryo-electron microscopy (cryo-EM), a technique that simplifies and improves the imaging of biomolecules. Similarly, the 2017 Nobel Prize in physiology or medicine was awarded to three NIGMS grantees for their work on molecular mechanisms controlling circadian rhythms, more commonly known as "biological clocks." Biological clocks influence a variety of physiological responses such as alertness, hunger, metabolism, fertility, and mood; clock dysfunction is associated with various disorders, including insomnia, diabetes, and depression. These awards serve as yet another testament to how investing in the study of fundamental biological processes can yield important insights into the principles that underlie human biology, health, and disease.

Because scientific breakthroughs generally cannot be predicted in advance and often originate from unexpected or disparate strands of knowledge, a cornerstone of NIGMS' strategic plan is to support a broad and diverse portfolio of fundamental research. This strategy builds the strongest possible foundation on which breakthroughs can arise.

**NIGMS STRATEGIC PRIORITY: NEW FUNDING APPROACHES TO ACCELERATE
SCIENTIFIC PROGRESS AND DISCOVERY**

In order to enhance the efficiency and productivity of fundamental biomedical research, the NIGMS has developed a new mechanism to fund scientists. The Maximizing Investigators' Research Award (MIRA) seeks to transform how fundamental biomedical research is supported by providing individual investigators with a heightened level of both scientific stability and flexibility.¹ These awards allow investigators to follow new research directions and insights in real-time, while simultaneously providing an extra year of support as part of a more coordinated scientific program (versus single project) focus. In addition, the peer review process for MIRA applicants reviews early stage investigators (ESIs) independently from established investigators (EIs), thus allowing each group of applicants to be examined relative to their own peer group.

Since the creation of the program, the NIGMS has awarded 231 MIRAs to EIs and 192 MIRAs to ESIs. The MIRA program is especially beneficial for ESIs, as evidenced by the increase in the number of ESI applications from 393 in 2015 (prior to MIRA) to 649 in 2017. The number of ESIs funded by the Institute per year has nearly doubled in the same time period. The NIGMS will continue to monitor the progress and outcomes of the MIRA program as it evolves.

Because some areas of biomedical investigation require groups of investigators to synergistically work together to solve complex problems, the NIGMS recently developed and implemented a new team-science support mechanism known as the Collaborative Program Grant for Multidisciplinary Teams.² This investigator-initiated funding opportunity supports multidisciplinary teams of researchers to work toward a shared goal that has the potential to have a major impact on one or more fields of biomedical research. Because this program only funds highly integrated research teams working toward a common objective, it will promote and enable a type of collaborative science that can't easily be supported through other kinds of research grants. Further, these new awards possess an optional component that allows for support of pilot projects by early-stage investigators to develop research in the team's area(s) of expertise with a goal of helping the junior researchers obtain independent funding.

NIGMS STRATEGIC PRIORITY: DEVELOP AND SUSTAIN A HIGHLY SKILLED, DIVERSE, and PRODUCTIVE BIOMEDICAL RESEARCH WORKFORCE

The NIGMS plays a leading role in supporting the career development and training of the next generation of scientists, including the development of institutional research capacities in regions across the country in which the levels of NIH support have been historically low.

Given the rapidly evolving landscape of science and medicine, the Institute is working to catalyze the modernization of graduate education. Recently, the NIGMS issued a new funding opportunity announcement (FOA) for its pre-doctoral T32 training grants³ that focuses on addressing several key issues such as: shifting the emphasis from simply teaching scientific “facts” to teaching both scientific and professional skills; developing the acumen needed to become rigorous and responsible scientists; supporting a safe, inclusive and diverse training environment; promoting the use of evidence-based teaching and mentoring practices; and enhancing student career development. Over the next several years, the NIGMS will work to implement this revised T32 program and will carefully evaluate its outcomes. In addition, the NIGMS is also working to ensure that emerging issues can be quickly incorporated and addressed in the training process, as appropriate. For example, the Institute has recently supported the development of open-access curricular training modules in areas related to improving the rigor and reproducibility of biomedical research. These modules are available on the NIGMS website,⁴ with more modules due to be added this year. The goal is to generate useful resources for graduate training programs.

Through its Institutional Development Award (IDeA) program, the NIGMS provides targeted support to help broaden the geographic distribution of biomedical research funding by enhancing the competitiveness of investigators located at academic institutions in states having a historically low level of NIH support. The IDeA Centers of Biomedical Research Excellence (COBRE), for instance, support thematic, multidisciplinary centers that expand and develop faculty research capabilities and research infrastructure, in part through the development of core technology

facilities needed to carry out modern multidisciplinary collaborative research. Another important aspect of the IDeA program is its support of medical research for rural and underserved communities. The IDeA Clinical and Translational Research Network (CTR), for instance, provides support for clinical and translational research that addresses conditions that have been traditionally higher among certain regions, populations or communities, including (but not restricted to) cancer, cardiovascular disease, and substance abuse disorders.

Because developing a well-trained research workforce begins with early outreach and education, the NIGMS was proud to welcome the NIH Science Education Partnership Awards (SEPA) to the Institute in 2017.⁵ SEPA supports diversity in the workforce by providing opportunities for students (specifically at the pre-kindergarten to grade 12 levels) from underserved communities to learn about careers in basic or clinical research. Ten of the fourteen SEPAs in IDeA states are currently in partnerships with IDeA COBREs or IDeA Networks of Biomedical Research Excellence (INBREs). An Institute goal is to fund at least one SEPA in every state.

NIGMS STRATEGIC PRIORITY: CREATE AND SHARE CUTTING-EDGE TOOLS AND RESOURCES

Given that technology plays a critical role in biomedical research, the NIGMS continues to place a high level of significance on supporting the development and dissemination of innovative, new technologies that have the potential to transform research. To this end, the NIGMS supports a multi-phased funding strategy that consists of support for an initial proof-of-concept phase for a given technology followed by potential support for a second prototype refinement phase. These phases can then lead to the adoption and expansion of the technology via commercialization through small business innovation research or small business technology transfer (SBIR/STTR) grants. Technologies can also be applied toward answering specific scientific questions through their incorporation into regular research project grants or, once sufficiently mature, through their incorporation into resources supported by the Institute's Biomedical Technology Research Resources (BTRR) program.⁶ Programs such as the BTRR form an important part of the NIGMS' portfolio as the Institute seeks to ensure broad access across the research community to cutting-edge technological resources. For example, synchrotron-based technologies, an extremely powerful source of X-rays, are critical for structural biology research; more than 90% of all three-dimensional structures of biological molecules in the Protein Data Bank⁷ were determined using data from synchrotrons. The NIGMS recently shifted its support for these important resources from research grants to a mechanism focused on user-access, utility and efficiency of operations. A similar model will be used to support the new national cryo-electron microscopy centers.

CONCLUSION

Mr. Chairman, in this statement, I have tried to highlight just a few examples of how NIGMS' programs maximize the scientific returns on the taxpayers' investments in fundamental biomedical research. As the scientific enterprise and national clinical landscape continue to evolve, the NIGMS looks forward to continuing to meet and address both the challenges and opportunities associated with this dynamic environment, and in so doing, to the many more advances that will emerge from institutions, laboratories, research teams, and individual investigators across the

nation. We thank you for your continued support and for this opportunity to describe some of the new initiatives at NIGMS

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Jon R. Lorsch, Ph.D. Director, National Institute of General Medical Sciences

Jon R. Lorsch, Ph.D., became the director of the National Institute of General Medical Sciences (NIGMS) in August, 2013.

Dr. Lorsch came to NIGMS from the Johns Hopkins University School of Medicine, where he was a professor in the Department of Biophysics and Biophysical Chemistry. He joined the Johns Hopkins faculty in 1999 and became a full professor in 2009.

A leader in RNA biology, Dr. Lorsch studies the initiation of translation, a major step in controlling how genes are expressed. When this process goes awry, viral infection, neurodegenerative diseases and cancer can result. To dissect the mechanics of translation initiation, Dr. Lorsch and collaborators developed a yeast-based system and a wide variety of biochemical and biophysical methods. The work also has led to efforts to control translation initiation through chemical reagents, such as drugs.

NIGMS supported Dr. Lorsch's research from 2000-2013. He also received grants from NIH's National Institute of Diabetes and Digestive and Kidney Diseases and National Institute of Mental Health, as well as from other funding organizations.

Dr. Lorsch is as passionate about graduate education as he is about research. During his tenure at Johns Hopkins, he worked to reform the curricula for graduate and medical education, spearheaded the development of the Center for Innovation in Graduate Biomedical Education, and launched a program offering summer research experiences to local high school students, many from groups that are underrepresented in the biomedical and behavioral sciences. In addition, he advised dozens of undergraduate and graduate students and postdoctoral fellows.

Dr. Lorsch received a B.A. in chemistry from Swarthmore College in 1990 and a Ph.D. in biochemistry from Harvard University in 1995, where he worked in the laboratory of Jack Szostak, Ph.D. He conducted postdoctoral research at Stanford University in the laboratory of Daniel Herschlag, Ph.D.

Dr. Lorsch is the author of more than 80 peer-reviewed research articles, book chapters, and other papers. He has also been the editor of six volumes of *Methods in Enzymology* and has been a reviewer for numerous scientific journals. He is the author on two awarded U.S. patents. His honors include six teaching awards from Johns Hopkins.

¹ <https://www.nigms.nih.gov/research/mechanisms/MIRA/pages/default.aspx>

² <https://grants.nih.gov/grants/guide/pa-files/PAR-17-340.html>

³ <https://grants.nih.gov/grants/guide/pa-files/PAR-17-341.html>

⁴ <https://www.nigms.nih.gov/training/pages/clearinghouse-for-training-modules-to-enhance-data-reproducibility.aspx>

⁵ <https://www.nigms.nih.gov/Research/DRCB/SEPA/Pages/default.aspx>

⁶ <https://publications.nigms.nih.gov/btrrs/searchresults.asp>

⁷ <https://www.rcsb.org/>

**PREPARED STATEMENT OF JOSHUA A. GORDON, M.D., PH.D.
DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH). I am excited to discuss NIMH's efforts to accelerate scientific progress that will improve our understanding of mental illnesses, fueling transformative care for the greatest public health impact.

FUNDING IMPACTFUL SCIENCE TO ALLEVIATE BURDEN

To help millions of Americans suffering from a mental illness, NIMH continues to ardently pursue its mission to transform the understanding and treatment of mental illnesses. In 2016, approximately 44.7 million U.S. adults suffered from a mental illness; of these, an estimated 10.4 million U.S. adults experienced serious mental illnesses (SMI). To balance the challenge of alleviating the burden of mental illnesses now, while supporting research that will inform future treatments and interventions, NIMH prioritizes excellent and impactful science and strives for a diverse research portfolio of short-, medium-, and long-term investments. For example, in the short term, efforts in suicide prevention research, such as screening and predicting risk in emergency departments, could result in significant decreases in suicide events. In the medium term, research on techniques to manipulate neural circuits could be applied to the treatment of mental illnesses in humans. In the long term, computational and theoretical approaches to psychiatry are needed to refine treatments.

EARLY IDENTIFICATION AND INTERVENTION

Each year, thousands of adolescents and young adults in the United States experience first episode psychosis. To explore methods for establishing early intervention programs to help people with psychosis, NIMH launched the Recovery After an Initial Schizophrenia Episode (RAISE) project, which clearly demonstrated that when coordinated specialty care was provided early in the disease, outcomes for individuals were superior to usual care, including symptom reduction, improvement in school and work functioning, and increased quality of life. Based on these findings, the Centers for Medicaid & Medicare Services extended Medicaid coverage for coordinated specialty care, and the Substance Abuse and Mental Health Services Administration (SAMHSA) set aside 10% of its Mental Health Block Grant allocation for each state to support evidence-based programs that target first episode psychosis. Today, over 200 CSC programs operate in 49 states.

Suicide is a potential consequence of mental illnesses and one of the leading causes of mortality in the United States. Suicide rates have increased since 1999, and nearly 45,000 Americans died from suicide in 2016. Recent studies show that most individuals who die by suicide have had recent contact with a healthcare provider, and that early identification of those at risk for suicide is key to prevention. To address this major public health concern, NIMH partners with the National Action Alliance for Suicide Prevention and supports its Zero Suicide initiative to support healthcare systems reduce suicide events. Another example of NIMH-funded work in this area is the ED-SAFE project, which demonstrated that universal screening for suicide risk among adults in emergency departments (EDs) doubled the rate of detection, and

ED-initiated interventions for high-risk adults decreased suicide attempts by as much as 30 percent.

In addition, researchers in the NIMH Division of Intramural Research Programs developed a brief pediatric suicide risk screening instrument; the four-item Ask Suicide Screening Questions (ASQ) is now used in medical facilities around the world. Additional examples of NIMH-funded research include the Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) study, which uses innovative approaches to suicide screening and assessment for youth in EDs. NIMH also supports collaborative research hubs, which aim to reduce the high suicide rates among American Indian and Alaska Native youth.

Similarly, NIMH recognizes the importance of early identification and intervention strategies for individuals with autism spectrum disorder (ASD). NIH-funded research has identified ASD risk markers within the first 12 months of age; early signs of behavioral differences correspond with genetic and environmental risk for ASD that appear to act before birth and alter the very early stages of brain development. However, a critical gap exists in translating these methods into practical screening tools that could be widely used to identify ASD early in life. NIMH plans to launch an initiative aimed at developing and validating new screening methods for ASD for use in infants (0-12 months of age) which could lead to novel transformative treatments that improve outcomes.

DEVELOPING EFFECTIVE AND TRANSFORMATIVE TREATMENTS OF TOMORROW

NIMH supports efforts to systematically and rapidly employ ‘lessons learned’ from research findings and clinical practice to improve patient care. To help narrow the gap between research and practice, the Mental Health Research Network (MHRN), a learning healthcare system that includes large-scale practical trials and services research, uses electronic health records large and diverse healthcare systems to improve delivery of effective treatments. The NIMH Early Psychosis Intervention Network (EPINET) is another learning healthcare system, which will focus on early psychosis treatment clinics by linking clinical sites. Like other learning healthcare models, the aim of EPINET is to share and compare data that will narrow the time gap for feedback and can help guide practice and ultimately improve mental health care. In addition, NIMH-funded research on mobile health (mHealth) technologies includes smartphone and texting approaches to help treat and monitor patients with mental illnesses. These methods are examples of how NIMH-funded research create opportunities for continuous evaluation and improvement of care.

It is ever important that we continue to support research focused on developing tools that can be used to study and treat mental illnesses. For example, NIMH co-leads the cutting-edge NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Maps of whole brains in action, the ability to identify thousands of brain cells at a time, and innovative brain scanners are just a few of the advances funded by this groundbreaking effort. In the past three years, research under the Initiative has advanced so rapidly that now many of the previously funded individual projects will receive expanded support to achieve the ambitious goals of the BRAIN Initiative.

Specifically, NIH recently announced funding for 110 new awards for the BRAIN Initiative. The new round of awards includes the BRAIN Initiative Cell Census Network (BICCN), aimed at providing researchers with comprehensive references of diverse brain cell

types to generate the knowledge necessary for understanding brain disorders, including mental illnesses. Additionally, new BRAIN Initiative research awards aim to address neuroethical issues associated with human brain research. Through the innovative studies supported by the BRAIN Initiative, researchers will be able to produce a revolutionary, dynamic picture of the brain that will lend to new ways to treat, cure, and even prevent mental illness.

Finally, NIMH has supported successful efforts to map the genes that predispose individuals to schizophrenia and other SMIs. Thanks to these efforts, we now know of hundreds of locations in the genome associated with risk for SMI. Each of these locations represents an important clue into the neurobiology of SMIs and holds promise as a potential therapeutic target. Current efforts, including the PsychENCODE consortium, which studies the relationship between genetic risk and protein expression in the brain, and an initiative that uses convergent neuroscience approaches to elucidate how these risk factors alter the function of neurons and circuits in the brain, are aimed at translating these genetic discoveries into new knowledge and novel treatments.

NIMH will continue to vigorously support research using novel approaches to enhance biological understanding, translation of evidence, services and intervention delivery, and therapeutics development, all aimed at reducing the tremendous burden shouldered by individuals and families living with mental illnesses.

Joshua A. Gordon, M.D., Ph.D.
Director, National Institute of Mental Health

Joshua A. Gordon, M.D., Ph.D. is the Director of the National Institute of Mental Health (NIMH), the lead federal agency for research on mental disorders. He oversees an extensive portfolio of basic and clinical research, the aim of which is to transform the understanding and treatment of mental illnesses, paving the way for prevention, recovery, and cure.

Dr. Gordon pursued a combined M.D.-Ph.D. degree at the University of California, San Francisco. Medical school coursework in psychiatry and neuroscience convinced him that the greatest need, and greatest promise, for biomedical science was in these areas. Dr. Gordon completed his psychiatry residency and research fellowship at Columbia University where he studied brain regions important for memory and emotional processes associated with anxiety and depression. He joined the faculty of Columbia Psychiatry Department in 2004 and maintained a general psychiatric practice, caring for patients who suffer from the illnesses he studied in his lab at Columbia.

Dr. Gordon's research focuses on the analysis of neural activity in mice carrying mutations of relevance to psychiatric disease. He employs a range of systems neuroscience techniques, including *in vivo* imaging, behavioral recordings, and optogenetics, which is the use of light to control neural activity. His research has direct relevance to schizophrenia, anxiety disorders, and depression.

**PREPARED STATEMENT OF ELISEO J. PÉREZ-STABLE, M.D.
DIRECTOR, NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH
DISPARITIES**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute on Minority Health and Health Minorities of the National Institutes of Health (NIH).

**ADVANCING THE SCIENCE OF MINORITY HEALTH AND HEALTH DISPARITIES
RESEARCH**

Today, revolutionary advances in biomedical science, such as the emergence of genomics, precision medicine, and health information technology hold greater promise to improve our nation's health than has ever before been possible. We are on the cusp of major scientific advances that will change how we think about minority health and health disparities. The mission of the National Institute on Minority Health and Health Disparities (NIMHD) is to lead scientific research to improve minority health and reduce health disparities. To accomplish this, NIMHD plans, coordinates, reviews, and evaluates NIH minority health and health disparities research and activities; conducts and supports research in minority health and health disparities; promotes and supports the training of a diverse research workforce; translates and disseminates research information; and fosters innovative collaborations and partnerships. As part of its charge to improve minority health and reduce health disparities, NIMHD is currently developing the 2018-2022 Trans-NIH Minority Health and Health Disparities Strategic Plan in collaboration with the other NIH Institutes and Centers and with input from community partners and key stakeholders. Once completed, this strategic plan will provide a blueprint to advance the direction and goals of minority health and health disparities research.

As the science of minority health and health disparities research evolves, a critical multidisciplinary approach is needed to focus on research studies that facilitate scientific advances to improve minority health and to reduce health disparities. Minority health research is the scientific investigation of distinctive health characteristics and attributes of minority racial and/or ethnic groups who are underrepresented in biomedical research in order to understand population health outcomes. Health disparities research is a field of study devoted to gaining greater scientific knowledge about the influence of health determinants, understanding the role of different pathways leading to disparities, and determining how findings translates into interventions to reduce health disparities. In order to ensure that all populations have an equal opportunity to live healthy and productive lives, NIMHD leads advancement in minority health and health disparities research and promotes a diverse scientific workforce reflective of the population.

RESEARCH

Advancing the science of minority health and health disparities requires scientific vision; that means building and developing evidence-based information that takes into account the social determinants of health and the places where we live, learn, work, and play. To meet the demands of keeping up with biomedical advances, NIMHD is strengthening research in minority health and health disparities; increasing opportunities for investigator-initiated research; strengthening the evaluation and reporting of minority health and health disparities research; and supporting the expansion of workforce diversity.

NIMHD promoted the fields of minority health and health disparities by developing and posting NIMHD's Research Framework, a transformative scientific agenda which addresses the complex influences on health and health disparities. Specifically, the Research Framework reflects an evolving conceptualization of factors relevant to the understanding and promotion of minority health and to the understanding and reduction of health disparities. The framework focuses on how these influences affect individuals, families, communities and society at large. It serves as a vehicle for encouraging NIMHD- and NIH-supported research that addresses the complex and multi-faceted nature of minority health and health disparities and guides researchers on where on the scientific spectrum their research fits.

NIMHD's increased emphasis on the science of minority health and health disparities has evolved into the three focused areas of clinical and health services research, integrative biological and behavioral research, and community health and population sciences. The Clinical and Health Services Research area generates new knowledge to improve health outcomes and quality of health care for minority and underserved populations within the context of everyday clinical practice. It examines the development of preventive, diagnostic and therapeutic healthcare interventions that can contribute to reducing health disparities and how precision patient-clinician communication may reduce health disparities. Moreover, it supports clinical research that generates new knowledge to improve health outcomes and quality of healthcare. For example, researchers found that childhood cancer survivors who reported greater well-being rated religion and spirituality of high importance, accessed specialized cancer services more regularly, and expressed a greater level of health care self-efficacy.

The Integrative Biological and Behavioral Research area examines research on how biological and behavioral mechanisms and pathways influence resilience and susceptibility to adverse health conditions that disproportionately affect racial and ethnic minority populations, persons of less privileged socioeconomic status, and other health disparity populations. Research examples in this area include genomic and epigenomic risk and protective factors; human microbiome contributions to health and disease; and mechanisms through which behavioral risk and protective factors influence the development of adverse health conditions by triggering adverse biological pathways. For example, research found that changes in DNA, as a consequence of environmental factors, can be used to accurately estimate gestational age. This novel measure of gestational age may be a useful tool in addressing persistent higher rates of low birth weights for some minority populations.

The Community Health and Population Sciences research area focuses on community engaged research and large studies of populations in a defined geographic area that reflect overall health of minority and underserved population groups. Community engagement refers to the active participation of community members in contributing to the research process in a partnership with investigators. Studies within this area examine causes, prevention, screening, early detection, and management of disease such as epidemiologic studies that identify and describe disease burden and risk factors in disparity populations; behavioral, sociocultural, and environmental influences on disease risks and outcomes; and research integrating the multiple determinants of health at the biologic, behavioral, and contextual levels and their interactions. In a study examining the perspective of older breast cancer survivors toward physical activity, researchers found that

physical activity programs should focus on cancer treatment related concerns and include strength training.

Innovative partnerships and collaborations are instrumental and essential to improve minority health and reduce health disparities. NIMHD supports research partnerships across NIH and the federal government with a goal to create synergistic research approaches to improve public health for health disparity populations. Partnerships conducted and supported by the NIMHD have created innovative studies into how to promote screening for breast, prostate, and pancreatic cancers; examine how children's experiences affect brain development; investigate the effects of environmental exposures — including physical, chemical, biological, social, behavioral, natural and built environments — on child health and development; understand the sources of persistent health disparities in overall longevity, cardiovascular disease, and cerebrovascular disease; and to eventually eliminate health disparities in dental care and oral/pharyngeal cancer.

BUILDING A DIVERSE BIOMEDICAL WORKFORCE

At the core of NIMHD's transformative scientific agenda is its commitment to building institutional research capacity and a diverse cadre of minority health and health disparities researchers. The Centers of Excellence program creates collaborative hubs for minority health and health disparities research among research institutions and local communities, which support early-career scientists as well as established investigators. The Research Centers in Minority Institutions program builds research capacity, supports a new generation of researchers from underrepresented populations through pilot funding, and funds established scientists to conduct cutting edge science in basic, behavioral or clinical research topics. The Research Endowment program provides funds to low resource academic institutions with a diverse student body and faculty to support endowments that will help to support a training or research capacity program to promote minority health and health disparities research.

NIMHD is committed to supporting and developing a diverse biomedical workforce. We support training grants across the spectrum of experience from pre-doctoral awards through mid-career awards. Moreover, NIMHD has enhanced opportunities for early-stage investigators by: expanding awards to help senior postdoctoral fellows and junior faculty-level candidates to become competitive for major grant support; providing fellowships to help less experienced researchers to become productive, independent investigators; and restructuring the NIMHD Health Disparities Research Institute to support career development for promising early-career minority health and health disparities research scientists.

CONCLUSION

NIMHD continues to advance the science of minority health and health disparities by building upon evidence-based research; developing researchers from underrepresented populations and retaining their diverse insights; and enhancing programs that create research infrastructure and train a diverse scientific workforce. Through this scientific research agenda, NIMHD's mission and vision will lead to discoveries that will promote health equity and ultimately improve minority health and reduce health disparities.

Eliseo J. Pérez-Stable, M.D.
Director, National Institute on Minority Health and Health Disparities

Eliseo J. Pérez-Stable, M.D. is Director of the National Institutes of Health's National Institute on Minority Health and Health Disparities (NIMHD), which seeks to advance the science of minority health and health disparities research. NIMHD is the newest institute at NIH and has a budget of \$303 million in FY 2018. NIMHD also promotes diversity in the biomedical workforce. Under this framework, the Institute conducts and supports research programs to advance knowledge and understanding of mechanisms to improve minority health, identifies and understands health disparities and develops effective interventions to reduce these disparities in community and clinical settings. NIMHD is the lead organization at the National Institutes of Health (NIH) for planning, reviewing, coordinating, and evaluating minority health and health disparities research activities conducted by NIH.

Prior to becoming NIMHD Director in September 2015, Dr. Pérez-Stable practiced general internal medicine for 37 years at the University of California, San Francisco (UCSF) before moving to NIH in September 2015. He was professor of medicine at UCSF and chief of the Division of General Internal Medicine for 17 years.

Dr. Pérez-Stable's research expertise spans a broad range of minority health and health disparities disciplines. His research interests include improving the health of racial and ethnic minorities and underserved populations, advancing patient-centered care, improving cross-cultural communication, and promoting diversity in the biomedical research workforce. For more than 30 years, Dr. Pérez-Stable led research on Latino smoking cessation and prevention interventions in the U.S. and Jujuy, Argentina, epidemiology of tobacco behavior among minority populations, tobacco biomarkers in subpopulations, cancer control behaviors, use of interpreters in medical care, and clinical, social and behavioral issues in minority aging. He has mentored over 70 minority investigators, published over 280 peer-reviewed articles and was elected to the National Academy of Medicine of the National Academies in 2001.

Dr. Pérez-Stable is a native of La Habana, Cuba and immigrated to the U.S. as a child. He earned his B.A. in chemistry in 1974 and M.D. in 1978 from the University of Miami and completed clinical training in primary care internal medicine residency and general internal medicine research fellowship at UCSF. Dr. Pérez-Stable practiced primary care internal medicine for 37 years at UCSF following a panel of about 200 patients at any given time. He also supervised and taught students and residents in the continuity ambulatory care clinic and on the medical service in the hospital setting.

**PREPARED STATEMENT OF WALTER J. KOROSHETZ, M.D.
DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND
STROKE**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH). NINDS research improves the diagnosis, treatment, and prevention of brain diseases and other nervous system disorders, and the Institute is the world's largest supporter of basic research to understand the normal brain, which drives progress against disease throughout the public and private sectors.

THE CHALLENGE OF NEUROLOGICAL DISORDERS

According to the Centers for Disease Control and Prevention, in the United States: *traumatic brain injury (TBI)* is the leading cause of death and disability in children and young adults and a major problem for the elderly (falls), about 795,000 *strokes* occur each year, *epilepsy* affects 3 million adults plus nearly half a million children, *dementia* is a growing public health challenge, and *chronic pain* is perhaps the most common of all medical problems, and a major factor in the opioid crisis. Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, and hundreds of other disorders, common and rare, also affect the brain, spinal cord, and nerves of the body. Because of the multiplicity of brain disorders and the extraordinary complexity of the brain, neurological disorders present the most daunting challenges in all of medicine. For most of these diseases, treatments are still far from adequate.

PROGRESS AGAINST NEUROLOGICAL DISORDERS

Historically, progress against neurological disorders has been slow, but the pace appears to be accelerating, with encouraging advances against several neurological disorders in recent years. As NIH has driven medical progress in general, NINDS basic research has provided the foundation for these recent advances against neurological diseases, and the Institute's translational and clinical research have also made major contributions. A few recent examples illustrate:

- Stroke – Two decades ago, NINDS-supported research showed that tPA therapy can restore blood flow to the brain following a stroke. For the first time, stroke became a treatable emergency, and the care system organized to take advantage. Building on NINDS funded research, clinical trials in 2015 showed that timely intervention with intravascular devices can directly clear a blocked brain artery in severe strokes when tPA does not restore blood flow, with striking clinical benefit. In 2018 the NINDS DEFUSE 3 clinical trial reported that a brain imaging method can identify people who may respond well beyond the current restricted time window for this intervention, now up to 16 hours, so many more people with strokes may benefit¹³. These recent results again transform emergency stroke treatment, and stroke care systems are now making these catheter-based treatments available in both urban and rural communities.

¹³ N Engl J Med. 378:708-718 2018

- TBI – The 2018 FDA marketing authorization of the first blood test to help in the diagnosis of concussion exemplifies the extensive NIH and DoD cooperation on TBI. NINDS funded the foundational basic science and clinical studies to the successful research team, and DoD supported the subsequent development and testing. The test could reduce the cost and radiation exposure from thousands of unnecessary CT scans.
- New drugs – Pioneering NIH-supported basic and translational research, and subsequent private sector development, led to FDA approval of the first disease-modifying drugs for two rare pediatric diseases, spinal muscular atrophy (SMA) and Batten disease. The FDA also approved the first drugs for primary progressive multiple sclerosis, for movement problems associated with Huntington’s disease, and a drug for amyotrophic lateral sclerosis (ALS). And researchers reported promising results for migraine, adrenoleukodystrophy, Niemann-Pick disease, and several other disorders.
- Dementia – A long-term NIH study with more than 15,000 people found that middle aged Americans who have vascular risk factors, including diabetes, high blood pressure and smoking, are more likely to suffer from dementia later in life¹⁴. The findings add to a growing body of evidence linking cardiovascular health to brain health. The hope is that managing vascular risk factors in middle age may slow or prevent the development of dementia, and there are hints that may be happening¹⁵.

DRIVING FUTURE PROGRESS

NINDS will continue to emphasize investigator-initiated research with rigorous peer review because of its proven track record. Complementing this core strategy, the Institute calls for research proposals to address unmet public health needs or exceptional scientific opportunities. Among the notable activities for the coming year:

- The opioid crisis – Through a series of workshops and discussions in 2017, federal agencies, the scientific community, and industry forged a partnership to accelerate the development of safe and effective, non-addictive treatments for pain. NINDS leads two key priorities of the plan— development of biomarkers (objective indicators) of pain and of a clinical trials network to use biomarkers for the development of non-addictive pain treatments. Together with the NIH Pain Consortium and the NIH Director’s Common Fund, NINDS is also targeting the key question of why acute pain leads to chronic pain for some people, well after the original cause of pain has been resolved.
- ADRDs – Through the National Alzheimer’s Project Act (NAPA), Congress recognized the impact of not just Alzheimer’s, but also Alzheimer’s disease-related dementias (ADRDs). Frontotemporal dementia (FTD) is the most common dementia in people younger than 60, and Lewy body and Parkinson’s dementias also have a major impact. The most common ADRD,

¹⁴ JAMA Neurology 74:1246-54 2017

¹⁵ New England Journal of Medicine 374:523-32, 2016

Vascular Cognitive Impairment and Dementia (VCID), like stroke, affects brain blood vessels. VCID is so intertwined with Alzheimer's disease that most elderly people with dementia have a combination of the two. NINDS leads several new and ongoing initiatives to understand and develop treatments for the ADRDS, working closely with the National Institute of Aging (NIA), which provides funding to a suite of these NINDS-led programs. NINDS also leads the ADRD summits that occur every third year, as mandated by NAPA.

- AMP PD – NINDS, Celgene, Verily, Pfizer, GlaxoSmithKline, Sanofi, the Michael J. Fox Foundation (MJFF), and the Foundation for NIH are launching the Accelerating Medicines Partnership for Parkinson's Disease (AMP-PD). This new addition to the NIH AMP program will identify and validate biomarkers and new therapeutic targets for Parkinson's disease, leveraging a treasure trove of data and resources supported over the past several years by NINDS, MJFF, and others.
- Pediatric concussion – An NINDS initiative will develop biological measures of persistent symptoms following pediatric concussion, which addresses the highest research priority identified by a 2016 NIH scientific workshop on pediatric concussion.
- Biomarkers – The lack of reliable biomarkers for most neurological disorders heightens the challenges of developing treatments and dissuades private sector investment. An NINDS initiative will support the advanced development and validation necessary to bring potential biomarkers to clinical practice, complementing the extensive early phase biomarkers discovery research that is already underway.
- BRAIN Initiative – NINDS is an enthusiastic leader of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. The Initiative is developing and applying new technologies to understand how circuits of interconnected nerve cells in the brain enable us to perceive, act, think, and learn, and what goes wrong in brain disorders. Remarkable new tools now enable researchers to identify all of the individual brain cell types, monitor activity of thousands of cells in a circuit at once in real time, precisely manipulate cells' activity, and non-invasively monitor and stimulate the human brain with increasing precision. As the Initiative continues, engaging these new opportunities to enhance research on pain and addiction is a high priority.

Finally, NINDS continues its longstanding emphasis on investigator-initiated basic research, which is yielding remarkable advances on many fronts in addition to circuits. Among the many findings this year, for example, research discovered unexpected links between bacteria and brain blood vessels, new roles of non-nerve cells in the brain, insights about how genes orchestrate brain development, the role of undetected seizure-like activity in Alzheimer's disease, how the gut conveys information to the nervous system, mechanisms of memory, and novel ways that nerve cells respond to stress. Which findings from basic research will launch the next advances against disease is not yet apparent. However, NIH basic research will surely continue to be the wellspring of progress for both the public and private sector.

Walter J. Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke

Walter J. Koroshetz, M.D., was selected Director of NINDS on June 11, 2015. Dr. Koroshetz joined NINDS in 2007 as Deputy Director, and he served as Acting Director from October 2014 through June 2015. As NINDS Director, Dr. Koroshetz directs program planning and budgeting, and oversees the scientific and administrative functions of the Institute. He has held leadership roles in many NIH and NINDS programs including the NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, the NIH Blueprint for Neuroscience Research, the Traumatic Brain Injury Center collaborative effort between the NIH intramural program and the Uniformed Health Services University, and the establishment of the NIH Office of Emergency Care Research. Additionally, Dr. Koroshetz serves as Chair of the Interagency Pain Research Coordinating Committee (IPRCC) and the Executive Committee for the NIH Pain Consortium.

Before joining NINDS, Dr. Koroshetz served as Vice Chair of the neurology service and Director of stroke and neurointensive care services at Massachusetts General Hospital (MGH). He was a professor of neurology at Harvard Medical School (HMS) and led neurology resident training at MGH between 1990 and 2007. Over that same period, he co-directed the HMS Neurobiology of Disease course with Drs. Edward Kravitz and Robert H. Brown.

A native of Brooklyn, New York, Dr. Koroshetz graduated from Georgetown University and received his medical degree from the University of Chicago. He trained in internal medicine at the University of Chicago and Massachusetts General Hospital. Dr. Koroshetz trained in neurology at MGH, after which he did post-doctoral studies in cellular neurophysiology at MGH with Dr. David Corey, and later at the Harvard neurobiology department with Dr. Edward Furshpan, studying mechanisms of excitotoxicity and neuroprotection. He joined the neurology staff, first in the Huntington's Disease (HD) unit, followed by the stroke and neurointensive care service. A major focus of his clinical research career was to develop measures in patients that reflect the underlying biology of their conditions. With the MGH team he discovered increased brain lactate in HD patients using MR spectroscopy. He helped the team to pioneer the use of diffusion/perfusion-weighted MR imaging and CT angiography/perfusion imaging in acute stroke.

**PREPARED STATEMENT OF PATRICIA A. GRADY, PH.D., RN, FAAN DIRECTOR,
NATIONAL INSTITUTE OF NURSING RESEARCH**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 Budget request for the National Institute of Nursing Research (NINR) of the National Institutes of Health (NIH).

INTRODUCTION

The mission of NINR is to promote and improve the health of individuals, families, and communities. In pursuit of this mission, NINR has set forth a bold, innovative scientific agenda in our strategic plan, "Advancing Science, Improving Lives." The plan, which incorporates long-standing focus areas of nursing science and 21st century solutions for improving the Nation's health, encompasses four focus areas, including symptom science, wellness, self-management, and end-of-life and palliative care; along with continued development of a 21st-century nurse scientist workforce, and finding ways in which technology and innovation can contribute across all these areas. I appreciate this opportunity to share some examples of NINR's research.

SYMPTOM SCIENCE: PROMOTING PERSONALIZED HEALTH STRATEGIES

Through its focus on symptom science, NINR supports research to develop new knowledge in biology and behavior to improve our understanding of symptoms such as fatigue, pain, and sleep disturbance. For example, NINR-supported investigators found a potential connection between the use of opioids to treat pain and the rate of healing for chronic wounds. They found that patients who had never received opioids healed more rapidly, and that patients receiving higher opioid doses, because they had a larger wound size or painful co-occurring conditions, had slower wound healing in comparison with those receiving lower doses or no opioids. Their findings raise important considerations on potential connections between symptoms, biological factors, and clinical management of pain and chronic wounds.

WELLNESS: PROMOTING HEALTH AND PREVENTING ILLNESS

In promoting wellness, NINR strives to build the science to understand and prevent chronic conditions, reduce burden for patients and caregivers, and eliminate health disparities. A recent NINR-supported study found that family caregivers of persons with Alzheimer's and related dementias (ARD) reported an average of seven new or worsening symptoms and signs in the care recipient, such as confusion, decreased activity, and agitation, over a six-month period. Understanding the range of symptoms that caregivers must respond to when caring for loved ones with ARD can guide the development of future educational materials and interventions. Other NINR-supported researchers are testing: a family-focused intervention to reduce the risk of type 2 diabetes and cardiovascular disease in Hispanics; the effectiveness of an intervention to reduce the rate of obesity in rural Alaska Native children; and an intervention to increase physical activity and reduce falls in older adults.

END-OF-LIFE AND PALLIATIVE CARE: THE SCIENCE OF COMPASSION

As the lead Institute for end-of-life research at NIH, NINR supports research to inform high quality care for individuals and their caregivers, improve management of pain and other advanced symptoms, and facilitate decision-making at all stages of illness, including at the end of life. With our support of the Palliative Care Research Cooperative (PCRC) group, we continue to build the science of end-of-life and palliative care by expanding this extensive network of over 400 multidisciplinary palliative care scientists to include over 160 clinical trial research sites across the U.S. NINR recently expanded its *Palliative Care: Conversations Matter*® initiative, which aims to raise awareness of pediatric palliative care, by developing a new Web feature profiling different members of the pediatric palliative care team, including a chaplain, a child life specialist, a nurse, a nurse-scientist, a pediatrician-researcher, and a social worker. This resource gives families insight into the array of providers and services available to support them and gives providers a glimpse into how teams work together.

SUPPORTING A 21ST CENTURY NURSING SCIENCE WORKFORCE

NINR has long-recognized the importance of supporting scientists at all career levels, particularly those at an early career stage. NINR supports a variety of training opportunities for scientists and trainees. In addition to funding extramural trainees, NINR sponsors a Symptom Methodologies Research Boot Camp, focused on precision health methodologies and the latest advances in various ‘omics’ such as genomics and microbiomics. NINR’s Summer Genetics Institute provides a foundation in molecular genetics to improve research and clinical practice for graduate students, faculty, and clinicians. NINR also provides on-line video training resources on its website to support an innovative workforce, from students to early- and mid-career scientists.

CONCLUSION

Thank you for this opportunity to share some of NINR’s recent accomplishments. We look forward to continuing to support nursing research to advance science, improve lives, and envision new pathways to improve health.

Patricia A. Grady, Ph.D., RN, FAAN
Director, National Institute of Nursing Research

Dr. Patricia Grady is Director of the National Institute of Nursing Research (NINR). Under her directorship, NINR aims to improve the health of individuals, communities, and populations across the lifespan. Research supported through NINR examines health care issues to develop an evidence base for delivery of high-quality, cost-effective care. Major areas of study include symptom management of chronic illnesses, risk reduction, quality of life, and palliative care and end of life issues.

Dr. Grady is an internationally recognized researcher. She was elected to the Institute of Medicine in 1999 and is a member of several scientific organizations, including the Society for Neuroscience, American Academy of Nursing, and the American Neurological Association. She is also a fellow of the American Stroke Association. She has published numerous articles and papers on hypertension, cerebrovascular permeability, and stroke.

Her numerous awards include receiving the honorary degree of Doctor of Public Service from the University of Maryland and being named the Excellence in Nursing Lecturer by the Council on Cardiovascular Nurses of the American Heart Association. Dr. Grady is a past recipient of the NIH Merit Award and received the Public Health Service Superior Service Award for her exceptional leadership. In 2005, Dr. Grady received Doctor of Science, Honorary degrees from the Medical University of South Carolina and Thomas Jefferson University, and Columbia University School of Nursing honored her with its prestigious Second Century Award for Excellence in Health Care. In 2008, Dr. Grady received a Doctor of Science, Honorary degree from the State University of New York Downstate Medical Center.

Before coming to NIH, Dr. Grady held several academic positions and served on the faculties of the University of Maryland School of Medicine and School of Nursing.

Dr. Grady earned her Bachelor of Science in Nursing from Georgetown University. She received her Master of Science in Nursing from the University of Maryland School of Nursing, and Doctorate in Physiology from the University of Maryland School of Medicine.

**PREPARED STATEMENT OF PATRICIA FLATLEY BRENNAN
DIRECTOR, NATIONAL LIBRARY OF MEDICINE**

Mr. Chairman and Members of the Committee: I am pleased to present the President's Fiscal Year (FY) 2019 budget request for the National Library of Medicine of the National Institutes of Health (NIH).

ACCELERATING BIOMEDICAL DISCOVERY & DATA-POWERED HEALTH

The National Library of Medicine (NLM) plays an essential role in catalyzing basic biomedical science through its cutting-edge data science and informatics research, comprehensive information systems, and extensive research training programs. As the world's largest biomedical library, NLM acquires, organizes, and delivers up-to-date biomedical information across the United States and around the globe. Millions of data scientists, health professionals, and members of the public use NLM's electronic information sources every day to translate research results into new treatments, products, and practices; provide useful decision support for health professionals and patients; and support disaster preparedness and response.

Leveraging its 180-year history of organizing and disseminating biomedical literature, NLM is committed to the application of emerging data science capabilities to challenges in biomedical research and public health. It will do this by expanding its data and information resources and providing leadership in both the acquisition and analysis of data for discovery. It will expand its core biomedical literature and genomic collections to include a broad array of health, clinical, and biological data types and make these data findable, accessible, interoperable, and reusable (FAIR) for research. NLM will enhance its research programs to systematically characterize and curate data describing complex health phenomena and to devise new methods to uncover the knowledge held in data. It will restructure its biomedical informatics training programs to address data science as they continue to foster excellence and support a diverse workforce. NLM will develop an efficient organizational structure to accommodate emerging directions in research and services.

RESEARCH IN BIOMEDICAL INFORMATICS AND DATA SCIENCE

NLM's research programs support pioneering research and development to advance knowledge in biomedical informatics and data science. Its research portfolio spans such areas as artificial intelligence, computational biology, clinical decision support, public health surveillance, visualization, and discovery mining in digital data sets. This research encompasses areas of high importance to NIH and society at large, and for audiences ranging from clinicians and scientists to consumers and patients.

Research in data science produces novel analytical approaches and visualization tools that help scientists accelerate discovery from data and translate these findings to clinical solutions. It also aims to solve problems consumers face in accessing, storing, using, and understanding their own health data and to produce tools that make precision medicine discoveries available and more understandable to patients. Biomedical informatics research is

yielding advanced analytical methods and tools for use against large scale data generated from clinical care, leading to fuller understanding of the effects of medications and procedures as well as individual factors important in the prevention and treatment of disease processes.

Recognized as a leader in clinical information analytics, NLM conducts intramural research in areas such as medical language processing, high-speed access to biomedical information, analysis and use of high quality imaging data, advanced technology for emergency and disaster management, health data standards; and analysis of large databases of clinical and administrative data to predict patient outcomes and validate findings from clinical research studies. Leveraging extensive machine learning experience and field-based projects, NLM is now advancing analytical tools and deep learning techniques for application in image analysis research.

NLM's biomedical informatics research also addresses issues in computational biology. Research creates new ways to represent and link together genomic and biological data and biomedical literature and produces analytic software tools for gaining insights in areas such as genetic mutational patterns and factors in disease, molecular binding, and protein structure and function.

BIOMEDICAL INFORMATION SYSTEMS FOR RESEARCH AND HEALTH

NLM develops and operates a set of richly linked databases that promote scientific breakthroughs and play an essential role in all phases of research and innovation. Every day, NLM receives up to 12 terabytes of new data and information, enhances their quality and consistency, and integrates them with other NLM information. It responds to millions of inquiries per day from individuals and computer systems, serving up some 100 terabytes of information, including genomic, chemical, and clinical trial data, as well as citations to more than 25 million journal articles in PubMed and more than 4.7 million full-text articles in PubMed Central.

NLM also offers sophisticated retrieval methods and analysis tools to mine this wealth of data, many of which grow out NLM's research and development programs. For example, NLM tools are used to mine journal articles and electronic health records (EHRs) to discover adverse drug reactions, analyze high throughput genomic data to identify promising drug targets, and detect transplant rejection earlier so interventions to help clinical research participants can begin more quickly. Data analysis tools also support complex analyses of richly annotated genomics data resources, yielding important molecular biology discoveries and health advances for applications to clinical care. Such applications demonstrate how the benefits of big data critically depend upon the existence of algorithms that can transform such data into information.

As a major force in health data standards for more than 30 years, NLM's investments have led to major advances in the ways high volume research and clinical data are collected, structured, standardized, mined, and delivered. In close collaboration with other HHS agencies and the Veterans Administration, NLM develops, funds, and disseminates clinical terminologies designated as U.S. standards for meaningful use of EHRs and health information exchange. The goal is to ensure that EHR data created in one system can be transmitted, interpreted, and aggregated appropriately in other systems to support health care, public health, and research. NLM produces a range of tools to help EHR developers and users implement these standards and makes them available in multiple formats, including via application programming interfaces (APIs).

ENGAGING THE PUBLIC WITH HEALTH INFORMATION

NLM uses multiple channels to reach the public with health information, including development of consumer-friendly websites, direct contact, and human networks that reach out to communities. Direct-to-consumer information is made available in lay language through MedlinePlus, which covers more than 1000 health topics. EHR systems can connect directly with MedlinePlus to deliver information to patients and health care providers at the point of need in healthcare systems. In collaboration with NIH Institutes and Centers (ICs) and other partners, NLM produces the print and online *NIH MedlinePlus* magazine, and its Spanish counterpart, *NIH Salud*.

The National Network of Libraries of Medicine (NNLM) engages 6,500 academic health sciences libraries, hospital libraries, public libraries, and community-based organizations as valued partners in conducting outreach to ensure the availability of health information, including from NLM services. The NNLM provides a community-level resource for NIH's *All of Us* program, ensuring a point of presence in almost every county in the US. NNLM partners with local, state, and national disaster preparedness and response efforts to promote more effective use of libraries and librarians and ensure access to health information in disasters and emergencies. NNLM also plays an important role in increasing the capacity of research libraries and librarians to support data science and improve institutional capacity in management and analysis of biomedical big data.

CONCLUSION

To conclude, through its research, information systems and public engagement, NLM supports discovery and the clinical application of knowledge to improve health. Its programs provide important foundations for the field of biomedical informatics and data science, bringing the methods and concepts of computational, informational, quantitative, social, behavioral, and engineering sciences to bear on problems related to basic biomedical and behavioral research, health care, public health, and consumer use of health-related information.

Patricia Flatley Brennan, RN, PhD
Director, National Library of Medicine

Patricia Flatley Brennan, RN, PhD, is the Director of the National Library of Medicine (NLM). The NLM is the world's largest biomedical library and the producer of digital information services used by scientists, health professionals and members of the public worldwide.

Since assuming NLM's directorship in August 2016, she has led the development of a new strategic plan for NLM, which emphasizes priorities for advancing research and workforce development in data science and enhancing the effectiveness of NLM information services as a platform for biomedical discovery and data-powered health. She has also positioned NLM in the forefront of trans-NIH collaborations to solve key strategic data management challenges, including the NIH Data Commons, which promotes cloud-based analysis of research data with effective identity and access management services to ensure privacy and security.

Dr. Brennan came to NIH from the University of Wisconsin-Madison, where she was the Lillian L. Moehlman Bascom Professor at the School of Nursing and College of Engineering. She also led the Living Environments Laboratory at the Wisconsin Institutes for Discovery, which develops new ways for effective visualization of high dimensional data.

Dr. Brennan is a pioneer in the development of information systems for patients. She developed ComputerLink, an electronic network designed to reduce isolation and improve self-care among home care patients. She directed HeartCare, a web-based information and communication service that helps home-dwelling cardiac patients recover faster, and with fewer symptoms. She also directed Project HealthDesign, an initiative designed to stimulate the next generation of personal health records. Dr. Brennan has also conducted external evaluations of health information technology architectures and worked to repurpose engineering methods for health care.

She received a master of science in nursing from the University of Pennsylvania and a PhD in industrial engineering from the University of Wisconsin-Madison. Following seven years of clinical practice in critical care nursing and psychiatric nursing, Dr. Brennan held several academic positions at Marquette University, Milwaukee; Case Western Reserve University, Cleveland; and the University of Wisconsin-Madison.

A past president of the American Medical Informatics Association, Dr. Brennan was elected to the National Academy of Medicine of the National Academy of Sciences in 2001. She is a fellow of the American Academy of Nursing, the American College of Medical Informatics, and the New York Academy of Medicine.