

**DEPARTMENTS OF LABOR, HEALTH AND
HUMAN SERVICES, AND EDUCATION, AND
RELATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2017**

THURSDAY, APRIL 7, 2016

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10:04 a.m., in room SD-138, Dirksen Senate Office Building, Hon. Roy Blunt (chairman) presiding.
Present: Senators Blunt, Moran, Cochran, Alexander, Cassidy, Capito, Murray, Durbin, Mikulski, Shaheen, and Schatz.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF FRANCIS S. COLLINS, M.D., Ph.D., DIRECTOR

ACCOMPANIED BY:

DOUGLAS LOWY, M.D., ACTING DIRECTOR, NATIONAL CANCER INSTITUTE

WALTER KOROSHETZ, M.D., DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

RICHARD HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING

CHRISTOPHER AUSTIN, M.D., DIRECTOR, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

NORA VOLKOW, M.D., DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

OPENING STATEMENT OF SENATOR ROY BLUNT

Senator BLUNT. The Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies will come to order.

Thank you all for being here. Thank you, Dr. Collins, for bringing your team and the other institute directors you have with you for appearing today before the subcommittee. No surprise to any of you from comments I've already made that I'm troubled by the NIH budget request, a request that reduces discretionary funding for medical research by \$1 billion. I certainly would not think that would be the way we would want to follow our effort last year to increase research by \$2 billion, and I'm confident, without asking you this, though I may ask it later, if you really want us to fulfill the request here, which would cut research by \$1 billion.

The increase we were able to make last year for the year you're working in now was really the first significant increase in over a decade. During that decade, based on your numbers, the real buying power of those research dollars had decreased by about 20 percent, and I'm glad we could make a step back in the right direction with the work that Senator Murray and I and the rest of the committee struggled with and produced what I thought was a big step in the right direction last year.

Certainly, the budget, as it's submitted, leans heavily on new mandatory spending proposals that would bypass the current spending caps. I think instead of making difficult funding choices, the administration here has come up with proposals that are unlikely to happen. It's a risky decision. It's a decision that I don't support and hope that at the end of this process our committee will not look at what the administration has asked for, but look at what we would hope to be able to do.

Mandatory spending largely has been put on autopilot when we go in that direction. I think it's a big obstacle to addressing debt issues and other issues because we just simply don't have to revisit it once we make it a mandatory topic.

Short-term mandatory funding for NIH, Senator Alexander and I have talked about it. A surge, a focus on specific projects might be different than that, but anytime you create a mandatory cliff, it's possible to go over the cliff, and we've seen that happen in these areas before.

Over the next 10 years, CBO, the Congressional Budget Office, estimates that mandatory spending will already increase from 13 percent of gross domestic product to 15 percent, and at the same time, they anticipate that discretionary spending will decrease by 1.3 percent of gross domestic product for our entire economy. I think that means it's even more important for us to be willing to put a structure together where we look at priorities. If everything is a priority, nothing is a priority, and the hard work of this committee, with really lots of talent on both sides of the aisle, is to figure out what we can do about those priorities.

After last year's significant increase in the National Institutes of Health, it's time to again make research funding a national priority. You can't develop a pattern, at least you can't develop an annual pattern, if you don't do something in year 2, and so year 2 becomes increasingly important.

I believe strongly in the promise of medical research and what that medical research does for individuals and families and the economy and taxpayers. It represents hope for millions of patients who suffer from everything from cancer to kidney disease, from Alzheimer's to autism. National Institutes of Health (NIH)-funded research has raised life expectancy and improved the quality of life for all Americans. It has the power to transform the U.S. economy in significant ways as well.

By 2050, according to figures from NIH, the cost to treat and care for those suffering from just Alzheimer's alone is anticipated to be \$1.1 trillion of today's dollars. Now, I think most of us have a hard time grasping with what \$1.1 trillion may be. You know, when you hear \$10 billion or \$100 billion or \$1.1 trillion, my guess is not much happens different in anybody's brain to distinguish the

difference, but to put it in perspective, \$1.1 trillion is twice what we currently spend to defend the country. So if you're putting your mind somewhere, every military base, every ship, every plane, every uniform, every paycheck for the Army, Air Force, Coast Guard, Marines, the Navy, the Reserves, the National Guard, and double all over the world, all over the world, and double that, that's what we would be spending on Alzheimer's in 2050 if research doesn't produce a different way forward.

I used this statistic in a speech this week where Senator Murray and I were being appreciated for what we were able to do here last year, and, you know, if with Alzheimer's you can delay onset by an average of 5 years, you would reduce that number by 42 percent and have great impact on the lives of people that would get Alzheimer's and maybe even greater impact on the caregivers that are so impacted by what happens with that. And that's just one thing. There are numbers that we could relate and we ask you to talk to us about on all of these issues, but hopefully we'll make a renewed commitment to what you're doing, but also we want to keep track of what you're doing, and I'm sure that's one of the reasons that you know you're here today. We'll have questions about how you're doing, what you're doing, and what you plan to do going forward as well as what is part of the budget request.

[The statement follows:]

PREPARED STATEMENT OF SENATOR ROY BLUNT

Good morning. Thank you, Dr. Collins and the other Institute Directors, for appearing before the Subcommittee today to discuss the National Institutes of Health's fiscal year 2017 budget request.

I am deeply troubled by the National Institutes of Health's budget submission to reduce discretionary funding for medical research by \$1 billion. Last year, this Subcommittee made great strides to begin to restore the NIH's buying power with a \$2 billion increase. This was the first significant increase for the National Institutes of Health in the Labor/HHS bill in over a decade. Yet the Administration's fiscal year 2017 request destroys this step forward by proposing a budget that reduces annual funding for the National Institutes of Health.

The Department of Health and Human Services submitted a budget that leans heavily on new, mandatory spending proposals to bypass current spending caps. Instead of making the difficult funding decisions necessary to live within the budget caps agreed to by the Administration less than 6 months ago, the Department decided to cut programs that receive bipartisan support in the hopes they would receive funding outside the annual appropriations process. This was a risky decision and one that I do not support.

The reliance on mandatory spending to supplant discretionary funding contributes to exactly what is wrong with our Federal budget. Mandatory spending, largely put on autopilot, is the biggest obstacle in addressing our national debt. Over the next 10 years, the Congressional Budget Office estimates mandatory spending will increase from 13 percent of Gross Domestic Product to 15 percent. Conversely, discretionary spending is expected to decrease 1.3 percent over the next decade. The annual appropriations process allows, and forces, Congress to address spending levels every year. It is the responsible way to address funding priorities. Further, reducing discretionary spending only to increase mandatory spending does nothing but remove the accountability of the appropriations process.

After last year's significant investment in the NIH, this is the time to make research funding a national priority. I strongly believe in the promise of medical research. It represents hope for millions of patients who suffer from conditions ranging from cancer to kidney disease. NIH-funded research has raised life expectancy and improved the quality of life for all Americans.

It also has the power to transform the U.S. economy. By 2050, the cost to treat and care for those suffering from Alzheimer's disease is expected to top \$1.1 trillion a year. To put this figure in perspective, this is twice what the Federal Government currently spends to defend the Nation.

Last year's funding increase cannot and should not be a one-time investment. A pattern is started in a second year, and I believe we must seize the opportunity this year to start a pattern of sustained increases for the National Institutes of Health. It is time for a long-term commitment to medical research.

Thank you for being here today.

Senator BLUNT. And I am pleased to turn to Senator Murray, who she and I have had really the first year we've had a chance to work closely together, and it's been a significant partnership for me.

STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Well, thank you, Mr. Chairman. It's good to work with you as well.

And, Dr. Collins, thank you for being here. We are so grateful for all you've done to champion the critical work of the NIH. You have been a great partner, and I really appreciate all of your team who is here today, and look forward to hearing from all of you.

The investments that we make here in this subcommittee really help keep our families and our communities healthy by supporting programs that reduce infant mortality, train doctors and nurses, provide care in rural communities, prevent the spread of infectious diseases, and so much more. The NIH accounts for the largest share of our subcommittee's resources, and its work is vital to all these efforts. The basic research that it supports leads to discoveries and breakthroughs that give hope to those living with chronic and life-threatening disease and help drive economic growth and competitiveness.

Today, the NIH is taking advantage of the achievements made in human genetics, neuroscience, and other fields to make major advances in our understanding of the human brain, and diseases like cancer and Alzheimer's disease. Its Precision Medicine Initiative is using the genetics of cancer to find effective therapies.

I recently heard from a woman named Janet in my home State of Washington who benefited from this focus on targeted treatment. Although she had been in good health, was a non-smoker, she was diagnosed with stage 3 lung cancer that quickly advanced to stage 4. With her treatment options exhausted, she learned online about a mutation testing opportunity, and that led to a treatment that successfully targeted her cancer mutation, and it saved her life. That was 3 years ago, and thankfully Janet's illness remains under control.

NIH's MATCH trial is taking the testing of cancer mutations to a national level with the hope that many more patients will be helped. The Vice President's Moonshot initiative will accelerate these efforts, expand access to clinical trials, and improve data sharing, all with the goal of saving more lives.

I'm really proud that my home State of Washington is home to several institutions that are on the cutting edge of this field. It includes the Fred Hutchinson Cancer Research Center, Seattle Children's Hospital, and the University of Washington, which are using Precision Medicine to tackle breast cancer, leukemia, and Alzheimer's disease, among others. Nearby, the Allen Institute is working with support from the NIH to map and unlock the secrets of the human brain. I recently visited there, and it is amazing.

We are on the cusp of major breakthroughs on so many of the illnesses that cost lives and hurt families each day, and I think we should make sure that our researchers and our scientists have all the tools and resources they need.

I know members on both sides of this aisle agree, so this is not a partisan issue. And I'm really pleased that in the recent budget deal, Democrats and Republicans were able to come together to boost discretionary investments in the NIH. That was really an important step forward, and I don't see any reason to stop there. That's why I've made very clear in my discussions with Chairman Alexander about legislation we're working on to advance medical innovation in the HELP Committee, that if we really want to get patients safer, more effective treatments and cures, we have to take advantage of every funding opportunity, including mandatory investments in the NIH. It is really a make-or-break priority.

So I remain hopeful that we'll be able to write a bipartisan appropriations bill in this subcommittee for fiscal year 2017 and continue strong support for NIH and the many other critical investments in this bill.

I'm also committed to working on a bipartisan agreement on our innovations package, my chairman is here on that, to build on the progress that we have made in the recent months with additional sustained funding.

Patients and families across the country are waiting and hoping for better cures and treatments, and here in Congress, we should do our part to deliver. So I really appreciate all the bipartisan work on this and look forward to working with everyone.

And, Mr. Chairman, thank you for holding this hearing.

Senator BLUNT. Thank you, Senator Murray.

Dr. Collins, it's wonderful to have you here, and your institute directors. If you would introduce everybody at the table with you, I would be pleased for you to do that. And then I look forward to your testimony.

SUMMARY STATEMENT OF DR. FRANCIS S. COLLINS

Dr. COLLINS. Thank you, Mr. Chairman. I'm happy to introduce my colleagues, starting to my left, your right.

Dr. Richard Hodes is the Director of the National Institute on Aging.

Dr. Walter Koroshetz, the Director of the National Institute of Neurological Disorders and Stroke.

Dr. Christopher Austin, the Director of the National Center for Advancing Translational Sciences.

Dr. Douglas Lowy, the Acting Director of the National Cancer Institute.

And Dr. Nora Volkow, who is the Director of the National Institute on Drug Abuse.

It's an honor to appear before you today. And before I begin, I want to thank this subcommittee for the recent \$2 billion boost in the fiscal year 2016 omnibus appropriation bill. That investment so energized our community and came at an unprecedented time of scientific opportunity, and we are truly grateful for your leadership.

Furthermore, I would be remiss not to acknowledge the efforts of many on this subcommittee who also serve on our authorizing committee, which marked up important and necessary new authorities for biomedical research just yesterday. That was very much appreciated.

So in this hearing on the last budget of this administration, and potentially my last opportunity to appear before you, I hope to reflect more broadly than usual on NIH's contribution to the Nation's health, so today I am going to break with a more cautious tradition and make some bold predictions, 10 areas in which I believe we can make major advances in the next 10 years given a sustained commitment of resources. So this is 10 for 10. So here we go.

First, the long arc of scientific discovery must begin with basic science. Just last week, all 27 NIH institute and Center directors and I published a letter in the *Journal of Science* to underline how essential it is for NIH to invest vigorously in basic research. That's how progress happens. Experiments that are going on right now in labs all across this Nation contain the seeds of breakthrough discoveries that will transform medicine. We don't know which ones they are, but we know they're there.

So let's fast-forward to 2026 and the first of our 10 breakthroughs. Advances in the detailed molecular analysis of individual cells. Cells are the unit of life. Cells are for biology like atoms are for chemistry. But through most of the long history of medical research, we've had very limited technical ability to study the intricate life of single cells. We've had to deal with millions of cells, sometimes billions. That's all changing with new technologies just invented in the last couple of years. That's just one example.

We can now decode the process by which individual immune cells attack and destroy healthy tissue in autoimmune disorders. We knew the immune system was involved, but now we can track each cell and see what it's up to, and then we can transform the ways we approach diseases like lupus and rheumatoid arthritis and many other conditions.

On to breakthrough number two. In 10 years' time, tools developed through the BRAIN Initiative, which I'm sure we're going to talk about this morning, have identified hundreds of different types of brain cells, and more than that, major circuits that are responsible for motor function, vision, memory, emotion, all functioning at the speed of thought. As a result, we will be able to diagnose neurological conditions earlier and more precisely and we'll have new targets to explore for prevention and treatment of conditions like autism, traumatic brain injury, prescription drug addiction, schizophrenia, and Parkinson's disease.

Number three. Aided by the BRAIN Initiative's new imaging techniques and discoveries made with our private sector collaborators, I believe we will be able in the next few years, Mr. Chairman, to identify individuals at high risk of Alzheimer's disease even before any symptoms appear, and, most importantly, provide them with effective therapies aimed at slowing or preventing the disease. Personal and family tragedies will be delayed or averted, and the economic savings from this alone will add up to hundreds of billions of dollars.

Number four. I predict that 10 years from now, safety testing for newly developed drugs, as well as assessment of the potential toxicity of numerous environmental exposures, will be largely carried out using human biochips that are loaded with cells accurately representing heart, liver, kidney, muscle, brain, and other tissues. This approach, made possible by the dramatic development of induced pluripotent stem cells, iPS cells, will mostly replace animal testing for drug toxicity and environmental sensing, giving results that are more accurate, at lower cost, and with higher throughput.

Prediction number five. Speaking of iPS cells, hope is also on the horizon for heart failure, a major cause of death in this country. Early experiments suggest that a patient's heart could even be rebuilt using his or her own iPS cells. This personalized rebuilt heart would make transplant waiting lists and anti-rejection drugs obsolete.

Number six. We will see the introduction of a safe and effective artificial pancreas. For those with diabetes, such a device will continually track changes in blood glucose levels and provide precise doses of insulin, significantly improving the management of their disease and preventing countless complications.

Number seven. New vaccines will be readily available. An effective Zika vaccine will have been developed and made widely available by 2018. Universal flu vaccines will protect against all strains of the virus, preventing that looming next worldwide pandemic and saving millions of lives, building on research just published last week. I'm also optimistic that an effective vaccine for HIV/AIDS will be available at last, giving us the opportunity to bring an end to this most frightening and costly global epidemic.

Prediction number eight. Genomics, neuroscience, and structural biology will collaborate to unveil entirely new targets for the treatment of pain, allowing researchers in the public and private sectors to develop highly effective, non-addictive medications for pain management. Having just attended and spoken at the Prescription Drug Abuse Summit last week, I can underline the urgency of reversing the alarming trend of opioid addiction in America, leading to 28,000 overdose deaths in 2014. We need new alternatives for pain management, and NIH and our partners will develop them.

Number nine. Ten years from now, we will have developed and broadly applied approaches to medicine that acknowledge not all people are the same, thanks in large part to the Precision Medicine Initiative and the more than 1 million volunteers that will have joined this unprecedented national research cohort. The willingness of these participants to share a wide variety of their health-related information will ensure that major new insights emerge, and Americans from all walks of life will be healthier than ever 10 years from now.

And, finally, for advance number 10, I predict that a decade from now, hundreds of thousands of individuals, like Janet in Washington, will be thriving, who, without NIH's research efforts, would have succumbed to cancer. Powerful new prevention strategies and targeted therapies will arise from the research described in the just published article which you see at your places, all of this accelerated by the Vice President's personal leadership of this Cancer Moonshot.

If that sounds bold, consider what's happening right now. Seven months ago, President Jimmy Carter revealed that melanoma had spread to his brain and that he was beginning a course of therapy to boost his immune system's ability to destroy his cancer cells. All of our hearts sank to hear that news. Last month, President Carter announced he is cancer-free and no longer needs treatment.

I could tell you a lot more stories like that of President Carter, but there are still millions out there waiting and hoping for a breakthrough to happen for them. At NIH, we seek to turn those hopes into reality. We are the National Institutes of Health, but we are also the National Institutes of Hope, and hope, wrote Peter Levi, in every sphere of life is a privilege that attaches to action. At NIH, we are all about action, and supported by this committee, who is also all about action, and your sustained efforts, we believe we can implement a strong, stable trajectory for NIH research, and the world can look forward over the coming decades to a healthier and happier future.

Well, thank you, Mr. Chairman. My colleagues and I welcome your questions.

[The statement follows:]

PREPARED STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D.

Good morning, Chairman Blunt, Ranking Member Murray, and distinguished Members of the Subcommittee. As you know, I am Francis S. Collins, M.D., Ph.D., and I am the Director of the National Institutes of Health (NIH). It is an honor to appear before you today to present the Administration's fiscal year 2017 budget request for the NIH, and provide an overview of our central role in enhancing the Nation's health through scientific discovery.

Before I discuss our diverse investments in biomedical research and the exciting scientific opportunities on the horizon, I want to thank this Subcommittee for the recent \$2 billion boost in the fiscal year 2016 Omnibus Appropriation bill. This investment comes at a time of unprecedented scientific opportunity and we are truly grateful for your leadership.

As the Nation's premier biomedical research agency, NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems, and to apply that knowledge to enhance human health, lengthen life, and reduce illness and disability. I can report to you today that NIH leadership, employees, and grantees continue to believe passionately in our mission.

As a Federal research agency, we are acutely aware that in order to achieve our mission we must be effective and efficient stewards of the resources we have been given by the American public. In December 2015, we released the NIH-Wide Strategic Plan, fiscal years 2016–2020: Turning Discovery into Health, an overarching, strategic plan that reflects the rapid progress in bioscience. This plan ensures our agency remains well positioned to capitalize on new opportunities for scientific exploration and address new challenges for human health. Developed after hearing from hundreds of stakeholders and scientific advisers, and in collaboration with leadership and staff of NIH's Institutes, Centers, and Offices (ICOs), the plan is designed to complement the ICOs' individual strategic plans that are aligned with their specific congressionally mandated missions.

The plan focuses on four essential, interdependent objectives that will help guide NIH's priorities over the next 5 years as it pursues its mission and optimizes return on public investment. The objectives are to:

- advance opportunities in biomedical research, from basic science to prevention and treatment;
- use all available information to set NIH priorities nimbly and wisely;
- enhance stewardship of the resources provided by the American people; and
- excel as a Federal science agency by managing for results.

Our strategic plan concludes with a bold vision of advances we will strive to deliver over the next 5 years including: enhanced survival of cancer patients from applications of precision medicine, critical steps toward universal flu and HIV vaccines, and crucial progress on the artificial pancreas that will lead to better management of diabetes. NIH will pursue these and many other forward-looking measures

to enhance our role as a visionary steward of the resources entrusted to us by the American people. Such actions will ensure that the U.S. biomedical research enterprise remains on the pathway to a bright and sustainable future.

Today, I want to share with you a few of the many promising opportunities before us that will lead to that healthier future for all. First, of all, many recent breakthroughs stem from our Nation's commitment to investing in basic science research. Basic science lays the foundation for advances in disease diagnosis, treatment, and prevention by providing the building blocks for clinical applications. Basic science is generally not supported in the private sector, and NIH's focus on understanding fundamental biological processes not only has led to no less than 145 Nobel Prizes to our grantees, but fosters innovation and ultimately leads to effective ways to treat complex medical conditions.

A compelling example of how we are trying to unravel life's mysteries through basic science is with the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which continues to address basic neuroscience questions. We are grateful to this subcommittee for its support of this initiative since its launch in fiscal year 2014, and we look forward to ramping this up further in fiscal year 2017. This bold, multi-agency effort to revolutionize our understanding of the human brain will enable the development and use of innovative technologies to produce a clearer, more dynamic picture of how individual cells and neural circuits interact in both time and space. By measuring activity at the scale of neural networks in living organisms, we can begin to decode sensory experience and, potentially, even memory, emotion, and thought. Ultimately, the technologies developed under the BRAIN Initiative may help reveal the underlying pathology in a vast array of brain disorders and provide new therapeutic avenues to treat, cure, and prevent neurological and psychiatric conditions such as Alzheimer's disease, autism, schizophrenia, epilepsy, traumatic brain injury, and addiction.

Scientific advances are also accelerating progress toward a new era of personalized medicine. President Obama announced the Precision Medicine Initiative (PMI) in January 2015, and we are thrilled to have a lead role in this multi-agency effort. As a long-term goal of this Initiative, NIH is building a national research cohort of one million or more volunteers who will play an active role in how their genetic, environmental, and medical information is used for the prevention of illness and management of a wide array of chronic diseases. Capitalizing on the alignment of scientific opportunities created by advances in genomics, the widespread adoption of electronic health records, the recent revolution in mobile health technologies, and the emergence of computational tools for analyzing large biomedical data sets, precision medicine is poised to usher in a new era in how we treat and diagnose disease. Ramped up funding in fiscal year 2017 will support several activities that are critical to the scope of the PMI Cohort Program, including enrolling and consenting participants, core phenotyping, expanded informatics, building a biorepository, and incorporating the use of wearable sensors. A cohort of this size will capture data on a wide range of diseases and be large enough to detect genetic and environmental effects that are difficult to discern from research on smaller groups. Scientists will be able to use data from this cohort to identify trends and understand health and disease on a much larger scale, and that will lead to new ideas for diagnostic tests, treatments, and prevention strategies.

A final area of exceptional scientific opportunity I want to highlight today involves one of our Nation's most feared killers: cancer. During his 2016 State of the Union Address, President Obama announced the establishment of the National Cancer Moonshot—a bold initiative to tackle this often life-threatening disease. Too many American families know all too well the devastation cancer can bring. More than 1.6 million new cases of cancer will be diagnosed and cancer will kill an estimated 600,000 Americans in 2016. With passionate and principled leadership from Vice President Biden, and in partnership with the Food and Drug Administration (FDA) and other Federal agencies, NIH's National Cancer Institute (NCI) is launching a bold and promising cancer research initiative to accelerate research to prevent, diagnose, and treat cancer. In fiscal year 2017, \$755 million in mandatory funds for new cancer-related activities are proposed at the Department of Health and Human Services (HHS). Within NIH, investments of \$680 million will support cutting-edge opportunities, such as prevention and cancer vaccine development, early cancer detection, cancer immunotherapy, genomic analysis of tumor cells, enhanced data sharing, and new approaches to pediatric cancer. Our sister agency, the FDA, will develop a virtual Oncology Center of Excellence to expedite the development of new diagnostics and therapeutics that will be safe and effective. We are at an inflection point in cancer research, and the science is ready for the concerted new effort this initiative will bring.

While all of these exciting research efforts and scientific opportunities are leading to a much deeper understanding of health and human disease, much more work needs to be done.

To this end, the President's fiscal year 2017 budget request for the NIH is \$33.136 billion, \$825 million or 2.5 percent above the enacted fiscal year 2016 level. This budget request reflects the President's and the Secretary's commitment to improving the health of the Nation and to maintaining our Nation's leadership in the life sciences. The request highlights investments in innovative research that will advance fundamental knowledge, and speed the development of new therapies, diagnostics, and preventive measures to improve public health, including an additional \$100 million to ramp up the PMI Cohort Program to a total of \$230 million, an increase of \$45 million for the BRAIN Initiative, bringing the total to \$195 million, and \$680 million for the National Cancer Moonshot.

The fiscal year 2017 budget request will enhance NIH's ability to support cutting-edge research and training of the scientific workforce. Within this budget, we will increase Research Project Grants (RPGs), NIH's funding mechanism for investigator-initiated research. NIH expects to support 36,440 total RPGs in fiscal year 2017, an increase of 600 above the fiscal year 2016 estimate. The budget request allocates resources to areas of the most extraordinary promise for biomedical research, while maintaining the flexibility to pursue unplanned scientific opportunities and address unforeseen public health needs.

I have provided you with examples of how investments in biomedical research through NIH are advancing human health, spurring innovations in science and technology, stimulating economic growth, and laying the groundwork for the future of the United States biomedical research enterprise. We have never witnessed a time of greater promise for advances in medicine than right now. With your support, the future of medicine can be very bright.

This concludes my testimony, and I look forward to answering your questions.

PREPARED STATEMENT OF DOUGLAS R. LOWY, M.D.

Mr. Chairman and Members of the Committee, I am pleased to present the President's fiscal year 2017 budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH).

NCI BUDGET OVERVIEW

The fiscal year 2016 budget that this subcommittee approved for NCI reflects a genuine understanding that this is a transformational moment for cancer patients and cancer research, and that the era of precision oncology is within reach. The \$70 million that you approved to fund the precision medicine for oncology initiative will foster a new era of medical practice where detailed genetic and other information about a patient's cancer is routinely used to deploy effective, patient-specific remedies to treat it. Other increases for fiscal year 2016 will allow NCI to broadly advance and successfully integrate the many disciplines necessary to improve outcomes for patients with all types of cancer.

For fiscal year 2017, NCI is advancing a new \$680 million initiative—known as the Cancer Moonshot Initiative—to accelerate progress across the entire field of cancer prevention, treatment, and discovery. However, in addition to the resources for the Moonshot initiative, NCI's \$5.9 billion budget supports a range of other research that is essential to achieving sustained progress in cancer. This includes:

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

Cancer Prevention: During fiscal year 2017 and beyond, preventing cancer and screening for cancer will remain a central priority for NCI. Prevention takes many forms, such as controlling tobacco use, vaccinating against cancer-causing infectious agents such as human hepatitis B virus and human papillomaviruses, limiting exposure to sunlight, and limiting exposure to asbestos and other carcinogens. These priorities have contributed to reducing the incidence and mortality rates for many cancers. NCI continues to invest heavily in cancer screening and prevention because we know that much more progress is possible for those at risk of cancer.

In parallel with our focus on prevention, NCI also will give increased attention to cancer health disparities—the differences in cancer incidence, prevalence, treatment response, and mortality among different population groups. Reducing and

eliminating cancer health disparities requires a deeper understanding of the complex interplay among a range of factors—biological, behavioral, environmental, and socioeconomic—that may contribute to the unequal burden of disease.

VICE PRESIDENT’S CANCER MOONSHOT INITIATIVE

For fiscal year 2017, NCI will launch a bold and promising cancer research initiative designed to make broad advances across a range of exciting opportunities to prevent, diagnose, and treat cancer. The resources supporting this fiscal year 2017 initiative will allow NCI to accelerate the pace of discovery in ways that produce tangible benefits for patients with all types of cancer, those at risk of cancer, and the growing population of cancer survivors.

The NCI budget justification identifies seven elements that form the core of the fiscal year 2017 initiative. These seven elements also can be organized into two broad themes: research on cellular analysis and research on novel approaches to prevent, diagnose, and treat cancer. In addition, some elements of the initiative contribute to both of these themes.

Theme I—Cellular Analysis: Three elements of the fiscal year 2017 NCI initiative support the cellular analysis theme.

A. Detecting Cancer Earlier: Even small tumors shed biomarkers into fluids of the body, such as the blood, saliva, and urine. Recent advances in genomic and proteomic technologies have greatly increased the sensitivity of methods to detect biomarkers in fluids, which raises the possibility of using such methods to screen for and identify cancers earlier. Such minimally invasive methods have recently been used for assessing whether cancer has recurred in individuals who were previously diagnosed and treated. The exciting new opportunity, for which NCI will use the resources in this fiscal year 2017 initiative, is to now apply these methods to cancer screening. The goal is to detect at a very early stage a range of cancer types for which we do not yet have effective screening methods and to improve the detection of cancer types for which screening is already established practice.

B. Research on Mutations: The resources in the fiscal year 2017 initiative also will allow NCI to support discoveries related to mutations and the mechanisms of cancer. Gaining a greater understanding of the mutations that occur within the cancer cell, the changes that occur within surrounding stromal tissues, and the nature of the immune system’s response to cancer will serve as a springboard to advance immunotherapy and targeted drug therapy.

Such research also can identify mechanisms used by cancer cells to co-opt the vascular tissue and other parts of the micro-environment near the cancer. Moreover, this approach can identify what type of immune response is already present, but may need a boost to combat the cancer. Coupling this information with the clinical response to drug therapy and immunotherapy could greatly enhance our understanding of the therapeutically relevant interplay between the tumor and the many cell types that surround it, leading to an increased ability to improve patient responses to treatment.

C. Speeding Progress on Childhood Cancers: Cancer in children poses unique challenges. Childhood cancers generally possess many fewer mutations than adult cancers and are less likely to have activation of enzymes known as kinases, which are the most frequent targets of cancer drugs for adult tumors. Furthermore, characteristic molecular changes that drive many childhood cancers arise in transcription factors and other cellular targets that are often considered “undruggable.” However, new technologies, built upon advances in chemistry that allow the preparation of libraries of small chemical molecules with a much more complex arrangement of molecular shapes, offer the promise of identifying inhibitors for the abnormalities found in pediatric cancers. The resources in NCI’s fiscal year 2017 initiative will support research such as this to deliver advances and treatments for pediatric cancers.

Theme II—Novel Approaches to Prevent, Diagnose, and Treat Cancer: Two elements of the fiscal year 2017 NCI initiative will advance the novel approaches theme.

A. Cancer Immunotherapy and Combination Therapies: For fiscal year 2017, NCI will provide increased support to promising research that employs the cells of the immune system to attack cancer. Immunotherapy is based on the principle that a patient’s immune system, when properly primed, can often detect and destroy cancer cells.

However, the challenge of immunotherapy is two-fold: first, tumors often effectively blunt anti-tumor immune responses, and second, the immune system must be successfully primed to recognize the tumor. Despite these challenges, during the past few years there have been some remarkable successes in overcoming these

problems. NCI is working to extend these early successes in cancer immunotherapy to virtually all tumor types through improved understanding of the mechanisms that enable and limit immunotherapy.

This element of the initiative will also support advanced research on combination therapies. Compared with single agent treatment, combinations of drugs that impair the growth and development of tumors along multiple molecular pathways are more likely to prevent the development of resistance and to produce long-lasting remissions. However, to benefit more patients, we urgently need to identify and understand the most effective combinations of targeted agents or targeted agents used in combination with immune-modulating molecules.

B. *Vaccines to Prevent or Treat Cancer:* Vaccines against cancer-causing infections can prevent certain cancers. The NCI research that led to pediatric vaccines to prevent infection with human papillomavirus (HPV)—and thereby prevent cervical and some other mucosal cancers—represents an important milestone in cancer prevention. The most advanced HPV vaccine prevents the infections that account for about 90 percent of these cancers. Cancer vaccine development will receive increased resources under NCI's fiscal year 2017 initiative.

Developing vaccines to treat early stage cancers and pre-malignant lesions not related to infections is another exciting opportunity that NCI will target with additional resources under the fiscal year 2017 initiative. Such vaccines can target unique or signature genetic changes found in cancers and premalignant lesions. Candidate lesions include those found in patients with early prostate cancer, patients with premalignant lesions such as ductal carcinoma in situ (DCIS) in the breast, and patients with genetic abnormalities that place them at high risk of colorectal cancer.

III—*Important Cross-Cutting Elements:* Finally, two elements of the NCI fiscal year 2017 initiative will broadly contribute to both of the themes identified above.

A. *Data Sharing to Speed Discovery and Verify Treatment Response:* Robust data science—managing enormous sets of molecular and clinical data—is essential in modern cancer research. “Big data” is a critical requirement for work that ranges from cancer genomics to research on cell signaling and to clinical trials, using efficient collection, storage, retrieval, analysis, and distribution of information. Without robust data science and a strong informatics infrastructure, the pace and scope of cancer research will be limited.

Establishing this advanced information technology capability will allow NCI to assemble tens of thousands of cases that have been carefully annotated with clinical and detailed molecular information. These shared bioinformatic resources will greatly increase our understanding of cancer and improve our ability to select the most appropriate treatment for patients.

B. *Exceptional Opportunities—Funding Other Promising Research:* The Exceptional Opportunities element of the initiative will allow NCI to capitalize on exciting scientific opportunities by awarding research funding—prioritized through a competitive process—to pursue innovative new ideas that target intractable problems in cancer science. NCI will examine novel opportunities in any area of oncology research ripe for expansion, from basic science, through translational approaches, to clinical trials. NCI will support Exceptional Opportunities research at academic sites and through public-private partnerships as a means of generating breakthrough results in cancer science and treatment.

THE ROLE OF NCAB

The National Cancer Advisory Board (NCAB) will provide advice and recommendations to NCI on the Moonshot initiative. In addition, on April 4, 2016, NCI announced the membership of a Blue Ribbon Panel of scientific experts, cancer leaders, and patient advocates as a working group of NCAB. The panel will share their insights on the scientific direction and goals for all elements of the initiative and offer recommendations on other compelling research opportunities. This will allow NCI to receive broad scientific counsel about the design and implementation of the initiative and its research and resource priorities, including the Exceptional Opportunities Fund.

We are eager to receive recommendations from NCAB and the Blue Ribbon Panel about the direction and emphasis for proposed research under the fiscal year 2017 initiative.

CONCLUSION

The NCI budget supports core, ongoing biomedical research that will advance scientific discovery and continue to reduce the burden of cancer in America. Our budget will also fund a compelling new initiative that offers the potential to accelerate

the rate at which we translate discoveries into cancer clinical practice and deliver benefits to patients.

Despite meaningful progress in recent years, too many Americans face a cancer diagnosis, and far too many die from the disease. There will be more than 1.6 million new cases of cancer in the United States during 2016, and more than 600,000 will die from cancer. As these statistics demonstrate, 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 fiscal year 2017 budget will allow NCI to advance our cancer research mission and deliver important results for the patients we serve.

PREPARED STATEMENT OF WALTER J. KOROSHETZ, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2017 budget request for the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH). NINDS supports research to better understand the brain and nervous system and to improve the diagnosis, treatment, and prevention of nervous system disorders. The burden of stroke, traumatic brain injury (TBI), dementia, chronic pain, epilepsy, Parkinson's disease, multiple sclerosis, and other all too familiar disorders of the nervous system is enormous. Hundreds of rare diseases add to the collective impact. The number, variety, and complexity of neurological disorders present formidable challenges, and the inaccessibility of the brain and its sensitivity to intervention compound the difficulty. Nonetheless, NIH research is delivering progress, directly and by catalyzing private sector investment. Moreover, with increasing recognition of commonalities among underlying disease mechanisms, progress against each disorder will spur advances against others.

STROKE, DEMENTIA, AND TBI

The United States' age-adjusted stroke death rate fell by 77 percent from 1969 to 2013, and NIH research is sustaining this trend.¹ In 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) showed that, for people with certain common risk factors, more stringent than usual blood pressure control lowered the risk of death from heart attack or stroke by almost a quarter, and in 2016 the Insulin Resistance Intervention after Stroke (IRIS) trial demonstrated that pioglitazone, a diabetes drug, prevents many recurring strokes in people with insulin resistance. Also last year, decades of public and private research led to the most significant advance in acute stroke care since NINDS clinical trials of the clot busting drug tPA showed that stroke is a treatable emergency. The recent results show that intravascular devices can remove an offending clot from a blocked brain artery and provide striking benefit when tPA alone does not restore blood flow in severe strokes. StrokeNet, a new clinical network, is investigating who should receive this intervention, and other stroke prevention and treatment trials are underway.

The National Alzheimer's Project Act recognized the impact of not just Alzheimer's disease, the most common dementia, but also Alzheimer's disease-related dementias (ADRDs). The National Plan to Address Alzheimer's Disease includes research recommendations from a 2013 NINDS-led summit on ADRDs, implementation has begun, and a follow up ADRD Summit in 2016 will continue to guide NIH dementia research. ADRD's include, for example, Lewy Body dementia, Parkinson's dementia, and frontotemporal dementia (FTD), which is the most common dementia in people younger than age 60. The most common ADRD, 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. The new NIH Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease (M2OVE-AD) Consortium will investigate how the brain's blood vessels contribute to dementias to identify new targets for treatment and prevention.

The growing recognition of intersections among stroke and VCID is encouraging in light of the progress in preventing stroke. Although increases in dementia loom as our population ages, there are indeed hopeful signs. In the Framingham Heart Study, the rate of dementia fell by 44 percent from the late 1970s to the early 2010s, and age of dementia onset was delayed by 5 years over that period.² What accounts for this progress is not fully understood, but converging evidence from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, the

¹JAMA 314:1731–1739 2015.

²New England Journal of Medicine 374:523–32, 2016.

Honolulu-Asia Aging study, the Atherosclerosis Risk in Communities (ARIC) study, the Northern Manhattan study, and other research suggests that controlling blood pressure reduces risk for cognitive decline in later life. A new public health campaign “Mind Your Risks” promotes controlling blood pressure for maintaining a healthy brain.

Nearly a century ago, physicians recognized another type of dementia, called dementia pugilistica, in boxers. In the modern era, neuropathologists are detecting this disorder, now called chronic traumatic encephalopathy (CTE), in autopsied brains of professional (and a few younger, amateur) athletes from contact sports. This has heightened the urgency of understanding the long-term consequences of mild TBI, or concussion, for the millions of people who have been exposed through sports, military service, or the risks of daily life. Despite decades of NIH research, including laboratory studies, brain imaging, and helmet impact monitoring in college athletes, many aspects of concussion are poorly understood. To augment ongoing research, NINDS and the Foundation for NIH’s Sports and Health Research Program, which was launched with a donation from the National Football League, established two multi-institution research consortia on CTE. In 2015, these neuropathologists took a major step forward by developing criteria that identify CTE and reliably distinguish it from other diseases in autopsied brain tissue. Studies applying these criteria on brains donated to brain banks for neurological disorders are reinforcing the concern that these long-term consequences of TBI may be more common than previously thought. The CTE consortia and a multi-site longitudinal study funded by NINDS in 2015 are addressing a major impediment to progress by testing brain imaging methods to diagnose CTE reliably in living people. A brain protein called tau, which accumulates abnormally in the brain in CTE, is the focus of a promising imaging method. Tau is also implicated in Alzheimer’s and other neurodegenerative disorders, reflecting the wider theme that abnormal protein degradation, accumulation, and propagation are involved in many brain diseases.

BRAIN CONNECTIONS AND BRAIN DISORDERS

Stroke and TBI are also among the many causes of the epilepsies, which are characterized by abnormal brain activity that causes seizures, and epilepsy-like brain activity may occur in Alzheimer’s disease. The epilepsies have many different causes. Hundreds of gene mutations cause epilepsy, including many identified by the NINDS Center without Walls (CWOW) on epilepsy genetics. Anti-seizure drugs, including ten that the NINDS Anticonvulsant Screening Program helped develop, can treat epilepsy. However, all epilepsy drugs have troublesome side effects, no existing drug modifies the underlying disease, and a third of people who have epilepsy do not respond well to any drug. A new CWOW will develop strategies to prevent epilepsy or to modify the disease process, rather than suppressing seizures.

Some diseases, like autism and epilepsy, are fundamentally disorders of brain cell activity and circuitry, and others, such as TBI, stroke, Parkinson’s, and Alzheimer’s disease, disrupt brain circuits as nerve cells or their connections are compromised. Despite our limited understanding of brain circuits and the imprecise technologies for altering brain cell activity in people, interventions that compensate for malfunctioning brain circuits produce remarkable results. Deep brain stimulation (DBS) dramatically reverses some symptoms for many people with essential tremor, Parkinson’s disease, and dystonia, and shows promise for epilepsy, Tourette syndrome, and several other disorders. Decades ago the NINDS Neural Interfaces Program led development of cochlear implants, which restore useful hearing to thousands of people by translating sound into electrical signals that brain circuits can interpret. More recently, that program pioneered devices that allow paralyzed people to control a robotic arm by commands directly monitored from their brains’ movement control circuits.

Better understanding of brain circuits and more precise means to control them would greatly improve these interventions and likely reveal unforeseen therapeutic strategies. Basic neuroscience research has made remarkable discoveries at the molecular level about how brain cells and synapses operate. And brain imaging, such as The Human Connectome Project, has driven advances in understanding how areas of the normal brain work together. Until recently, however, researchers have had limited tools to map the intricate synapse by synapse structure of brain circuits or to monitor or control the activity of the large numbers of nerve cells in a working brain circuit. New methods are essential to understand precisely how brain circuit dysfunction underlies brain diseases. The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is providing scientists with tools that are transforming understanding of how circuits work. Researchers have already, for example, turned on and off specific memories in laboratory animals, and found im-

portant clues to what goes wrong in movement control circuits in Parkinson's disease. Public-private partnerships have been facilitated to develop and test cutting edge stimulation and recording technologies for patients with epilepsy and Parkinson's disease.

PEOPLE

NINDS carries out its mission within an ecosystem that includes the public, non-governmental organizations, for profit companies, and the academic research community. NINDS engages all stakeholders in strategic planning and planning for specific diseases and issues, including health disparities and workforce diversity. NINDS also works closely with other parts of NIH and with other Federal agencies. The Federal Interagency TBI Research Informatics System (FITBIR) and the Center for Neuroscience and Regenerative Medicine (CNRM), for example, are among the many ways NIH and the Department of Defense cooperate on TBI. NINDS relies heavily on investigator-initiated research, which harnesses the insight and ingenuity of the U.S. research community, because of its track record of stimulating breakthroughs. When gaps are compelling, NINDS targets resources to unmet mission-critical scientific opportunities and public health needs. Among the many examples are the NeuroNext clinical network, which carries out early phase clinical trials of therapies from the academic or private sector, and centers or consortia in epilepsy, Parkinson's disease, autism, muscular dystrophy, and TBI. Policies and resources, such as brain banks, data centers, and gene and tissue repositories, enhance the research possible for individual researchers and promote sharing. To maximize research value, NINDS is among the leaders in advocating transparency of reporting and reproducibility of research, engaging researchers, peer reviewers, journal editors, trainees, and NIH staff.

Because the private sector is often reluctant to tackle neurological disorders, NINDS supports preclinical therapy development. These programs have recently, for example, developed candidate drugs, gene therapy, or biologics for ALS, muscular dystrophy, brain tumor, and stroke to readiness for clinical testing. From its inception, NINDS has played an indispensable role in rare disease research. Programs now bring academic disease experts together with drug development resources and knowhow. A current project, for example, is developing drugs for familial dysautonomia. It reflects a 23-year journey that identified the genetic cause, developed a screen for at-risk populations, engineered a mouse model, and screened for drugs that reverse symptoms in mice. The first drug for this disease is now in clinical trials. As the first therapies for several rare disorders are moving to clinical testing, NINDS is promoting clinical trials readiness, and NeuroNext is poised to expedite early phase trials.

Physicians and scientists in the public and private sector agree that basic research is essential for progress against neurological disorders, but without government support, basic neuroscience would scarcely exist. Some shift toward more applied research is appropriate given the remarkable opportunities arising from basic research. However, an extensive NINDS analysis revealed a decline over several years in the number of grant applications for fundamental research on the healthy brain. The Institute is holding the line against that trend, including targeted support with set-aside funds. The BRAIN Initiative reinforces NINDS emphasis on basic research and innovation. In fiscal year 2016, NINDS also launched the Research Program Award (RPA) to spur innovation, especially in basic research. The RPA application, review criteria, and award duration accentuate the investigators' promise and the long term significance of the proposed research program, rather than the details of proposed experiments.

Finally, NINDS must recruit and develop the best scientists and physicians from the full breadth of the Nation's talent pool. NINDS supports an array of training and career development opportunities to attract a vibrant and diverse scientific workforce. The inherent allure of understanding the brain attracts many of the brightest students, as do the prospects for progress against neurological disorders, which have never been so encouraging. Whether people will embark on training for scientific careers depends on their perception of the Nation's commitment to supporting research in the future.

PREPARED STATEMENT OF RICHARD J. HODES, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2017 budget request for the National Institute on Aging (NIA) of the National Institutes of Health (NIH).

Census data indicate that the number of Americans ages 65 and older, currently estimated at over 43 million strong, will likely double by 2040. Because aging remains the single most important risk factor for most chronic diseases and degenerative conditions in adults, it is imperative that we pursue a comprehensive national effort to understand aging and to develop interventions that will help older adults enjoy robust health and independence, enabling active engagement with their families and communities.

NIA leads this effort in 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 addition, we are the lead Federal agency supporting research on Alzheimer's disease (AD).

RESEARCH ON ALZHEIMER'S DISEASE

Data from several recent studies suggest that the rate of dementia, including AD, is actually decreasing. For example, researchers with the long-running Framingham Heart Study found that there was a progressive decline in incidence of dementia at a given age, with an average reduction of 20 percent per decade since the 1970s. The decline was more pronounced with a subtype of dementia caused by vascular diseases, such as stroke, and was observed only in persons with high school education and above. These results are consistent with findings from other recent studies in the United States and Canada, and it is our hope that as we identify factors that contribute to this unprecedented decline, we will also identify potential preventive strategies or even clarify the disease process itself.

Despite this promising trend, however, it is estimated that as many as 5.2 million Americans currently have the most common form of dementia—Alzheimer's disease. Scientists agree that unless the disease can be effectively treated or prevented, the numbers of people affected will increase significantly if current population trends continue. And in addition to the severe medical and psychological costs to patients and their families, AD and related forms of dementia impose significant societal and individual economic costs. One recent NIA-funded study found in the last 5 years of life, total healthcare spending for people with dementia was more than a quarter-million dollars per person, some 57 percent greater than costs associated with death from other diseases, including cancer and heart disease.

As the Federal lead on Goal 1 of the National Action Plan to Address Alzheimer's Disease—Prevent and Effectively Treat Alzheimer's Disease by 2025—NIA continues to move forward on a number of fronts, informed by input from researchers and advocates worldwide from the February 2015 Alzheimer's Disease Research Summit, the 2013 Summit on Alzheimer's-Related Dementias, and other key scientific conferences and emerging research findings. Additional funds directed to Alzheimer's in recent years are being used to accelerate research identifying new risk and protective genes; development of new cellular models of the disease to enable rapid screens of hundreds of thousands of molecules for potential as therapeutic agents; establishment of translational centers that will develop and apply cutting-edge approaches to drug development; population studies of trends in the incidence and prevalence of dementia; development of novel interventions to support dementia caregivers; and trials of therapies in people at the highest risk of disease.

Other researchers are repurposing existing compounds for use in AD. For example, investigators funded by NIA and the National Center for Advancing Translational Sciences found that AZD0530, a compound that has been used experimentally to treat some solid tumors, reversed memory loss and pathology characteristic of AD in a mouse model and is a promising candidate to test in humans with the disease.

Notably, in September/October 2015, NIA released a series of 10 Program Announcements (PAs) soliciting funding applications across the spectrum of AD research. These requests for applications offer opportunities for investigators in virtually every aspect of AD research—from basic biological studies to epidemiology to caregiving to clinical trials. The initial response to these PAs was extremely robust, and initial awards are anticipated for late fiscal year 2016.

Alzheimer's is also a primary focus of NIH's Accelerating Medicines Partnership (AMP), a joint public-private partnership to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets of disease. In March 2015, AMP-AD launched its Alzheimer's Big Data Portal and concomitantly released the first wave of data through this new resource, facilitating sharing and analyses of large and complex biomedical datasets. This approach will enable the development of predictive models of AD and the selec-

tion of novel targets that drive the changes in molecular networks leading to the clinical signs and symptoms of the disease.

NIH's plans, priorities, and recent accomplishments for Alzheimer's research are presented in our first Bypass Budget for Alzheimer's Disease and Related Dementias, in response to a Congressional directive.³ This comprehensive professional judgment proposal for fiscal year 2017, which was developed without taking into account the full range of resource constraints and competing priorities that the President's Budget must consider, was released in July 2015 and will be updated annually, informed by expert input from several key sources.

ADVANCES IN AGING RESEARCH

NIH supports research aimed at improving our understanding of the changes seen with aging at the physical, cognitive, behavioral, and social levels, as well as development of interventions to prevent or ameliorate age-related disease and dysfunction. For example, NIA-supported investigators recently found that naturally-occurring senescent cells that accumulate in the body shorten lifespan in mice, and that removing those cells delays age-related organ dysfunction. This finding aligns with previous research and provides additional support for the hypothesis that removal of senescent cells may be an effective approach to extending healthy lifespan.

NIA coordinates the NIH GeroScience Interest Group (GSIG), which was established in 2012 to accelerate and coordinate efforts to promote further discoveries on the mechanisms that link aging biology to the etiology of multiple chronic diseases and conditions, by developing a collaborative framework that includes multiple NIH Institutes. In October 2013, the GSIG and several private-sector partners convened a national Summit entitled "Advances in Geroscience: Impact on Healthspan and Chronic Disease." This meeting drew over 500 expert participants from around the world and led to the publication of a position paper in *Cell*, one of the world's leading journals on basic research, in 2014. A second Geroscience Summit is planned for April 2016 in collaboration with the New York Academy of Sciences and others.

NIA also continues to support its flagship studies on aging. As it approaches its sixtieth anniversary, the groundbreaking Baltimore Longitudinal Study of Aging (BLSA) continues its work toward identifying the longitudinal physical and cognitive changes that define aging; identifying the factors that affect the rate of age-related change; and understanding the relationship between aging and chronic disease. BLSA investigators are particularly interested in "exceptional agers"—those rare individuals who live well into their eighties with few health problems. In addition, this year the Health and Retirement Study (HRS) will complete 25 years of data collection and will implement several enhancements: addition of respondents representing the "Late Baby Boom" born 1960–1965; deployment of an improved approach to assessing cognitive impairment and dementia; and expansion of 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 and other future work also has the potential to reveal the biological pathways through which differences between social and demographic groups 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, a recent clinical trial identified several interventions directed at primary care clinicians that reduced the number of inappropriate prescriptions for antibiotics for acute viral respiratory tract conditions, an important cause of population-level antibiotic resistance. These interventions—which involved prompting a clinician to record a justification for prescribing antibiotics or comparing the clinician's performance to others in their region—may be useful tools to improve quality of care.

In another recent study, the Systolic Blood Pressure Intervention Trial (SPRINT), reducing systolic blood pressure to less than 120 mm Hg, as compared with less than the current standard target of 140 mm Hg, resulted in lower rates of major cardiovascular events and death from any cause among patients at high risk for cardiovascular events but without diabetes. Of particular note is the age of the SPRINT participants: all were over 50, and 28 percent were over 75. SPRINT was supported by NIA and several other NIH Institutes.

Serious injuries from falls, such as broken bones or traumatic brain injury, are a major reason for the loss of independence among older people. In 2014, the NIA partnered with the Patient-Centered Outcomes Research Institute (PCORI) to support a large, multi-center clinical trial to test individually tailored interventions to prevent fall-related injuries. The study, which is scheduled to conclude in 2019, is

³ <https://www.nia.nih.gov/alzheimers/bypass-budget-fy2017>.

ongoing and involves the NIA-funded Claude D. Pepper Older Americans Independence Centers.

Finally, NIA has continued to grow its award-winning Go4Life exercise and physical activity campaign. This effort centers on an interactive website, which features an evidence-based exercise guide in both English and Spanish, exercise videos, “virtual” coaches, and more. Over 350 partners at both the local and national levels use these resources in their community activities with seniors. September 2015 was designated national Go4Life Month. Partners sponsored over 600 activities in communities across the United States, culminating in a Capitol Walk in Washington, D.C., in which a corps of older adults joined Dr. Hodes, U.S. Surgeon General VADM Vivek H. Murthy, M.D., M.B.A., fitness expert Donna Richardson, and leaders from a number of agencies and organizations for a walk around the National Mall.

EMPOWERING THE NEXT GENERATION OF SCIENTISTS

As the number of older Americans continues to grow, we must not only increase the number of practicing physicians trained in geriatrics and relevant subspecialties but also 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 solicited applications for new training programs for joint M.D.-Ph.D.s 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.

PREPARED STATEMENT OF CHRISTOPHER P. AUSTIN, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President’s fiscal year 2017 budget request for the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH).

TRANSLATION

NCATS defines translation as the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public—from diagnostics and therapeutics to medical procedures and behavioral changes. An overarching need to translate research discoveries more efficiently and effectively led to the creation of NCATS. NCATS is advancing the relatively new field of translational science, through which investigators seek to understand the scientific and operational principles underlying each step of the translational process. These efforts serve as a basis for system-wide improvements in translational efficiency and effectiveness to ultimately get more treatments to more patients more quickly.

Following are examples of NCATS programs directed at overcoming major scientific and operational bottlenecks in the translational research process.

TRANSFORMING THE NATION’S CLINICAL RESEARCH NETWORK CAPACITY

NIH’s Institutes, Centers and Offices have a long, distinguished history of funding landmark clinical trials including those for coronary bypass surgery, treatments for breast cancer, and anti-retroviral drugs for people at high risk for HIV/AIDS infection. NCATS is addressing issues common to all clinical trials including approval and oversight of research protocols and timely participant recruitment, which have often resulted in high cost burdens for studies and frequent delays in implementation. These problems have led some investigators and companies to conduct their research outside of the United States, and this threatens our Nation’s innovative capacity and competitiveness, reduces economic opportunities, and deprives patients of the option to participate in research. In addition, when clinical investigators set up a clinical trial, they often create agreements and processes from scratch and abandon those tools at the end of the study, rather than making use of the existing structure and agreements for any future studies.

To address these pitfalls and inefficiencies, through its Clinical and Translational Science Award (CTSA) Program, NCATS has launched several initiatives designed to work together to strengthen and streamline our Nation’s network capacity to conduct clinical research. There are more than 50 CTSA Program medical research in-

stitutions across the country that serve as clinical and translational research hubs. Hub investigators collaborate to support high-quality clinical and translational research locally, regionally and nationally, fostering innovation in training, patient involvement and new methodologies.

NCATS is expanding the networking capacity of the CTSA Program with the addition of Trial Innovation Centers (TICs) and Recruitment Innovation Centers (RICs) that address key roadblocks to high-quality, harmonized, accelerated, efficient and effective multisite clinical trials. Through TICs, investigators will explore innovative approaches in streamlining trial implementation and disseminate best practices. RICs are intended to improve participant recruitment into clinical trials by using innovative means to assess the availability of potential participants and to enroll them in a timely manner. NCATS will make TIC and RIC awards later in fiscal year 2016. When fully implemented, these centers will be crucial resources for NCATS' CTSA Program clinical trial innovation network. By making the clinical trial network available to any investigator or organization wishing to conduct a clinical trial, the CTSA Program will benefit all clinical research, including that of other NIH Institutes and Centers (ICs), as well as other government, industry, academic, and patient advocacy group sponsors.

INNOVATION TO ADVANCE PRE-CLINICAL TRANSLATIONAL SCIENCE

Too often, the laboratory tests that scientists conduct during the pre-clinical phases of the translational process—research on a drug or other intervention conducted prior to testing in humans—fails to predict the safety and effectiveness of a treatment in humans. NCATS is studying, and developing solutions to overcome, the scientific and operational roadblocks in this part of the translational research spectrum as well.

An example is the Tissue Chip for Drug Screening program, which supports the creation of bioengineered devices to improve the process of predicting whether drugs will be safe and effective in humans. NCATS collaborates with the Defense Advanced Research Projects Agency (DARPA) and FDA to support the development of these three dimensional (3-D) platforms, sometimes called tissue chips or organs-on-chips, engineered to mimic the structure and function of living human tissues. Since the program's inception in 2012, scientists have developed more than 10 different types of individual organ chips. The program is now focused on integration of organ chips, making it possible to model the complexity of organ-to-organ interactions in response to drugs. One such success was the creation of EVATARTM, a miniaturized 3-D representation of the female reproductive tract and liver on a handheld, interconnected platform. This advance required a team effort of scientists from Northwestern University, Charles Stark Draper Laboratory and the University of Illinois at Chicago (UIC) collaborating to design the model for use in drug testing and to study the basic biology of female reproduction. The current success of the Tissue Chip is indicating future directions for the NCATS program, with some investigators already using the technology to develop disease models on chips to both understand the basis for diseases and identify treatments for them.

In a complementary program, NCATS is developing 3-D bioprinted human tissues to be used in the earliest stages of drug discovery. This initiative has the potential to accelerate the drug discovery process, enabling treatments to be developed faster and at a lower cost by bridging the predictability gap between the lab test and the test in humans. The manufacturing technique used to build live tissue structures results in a product that mimics natural live tissue. Live cells are harvested and dispensed into spatially-controlled patterns, layer-by-layer, to generate 3-D arrangements. These structures undergo further biological treatment until they form tissue-like structures. The ability to develop 3-D tissue structures on demand will enable the generation of data that are more relevant to the whole body response than traditional means, which use two-dimensional, single-layer cell cultures grown on plastic plates.

Of all translational tools, the most enabling is information, so NCATS also is developing a variety of informatics resources to collate and disseminate data that will help advance translational research. For example, using the flexible funding mechanisms available through NCATS' Cures Acceleration Network (CAN), NCATS is developing a breakthrough translational informatics "matrix" that will incorporate data about all diseases, including signs, symptoms, signaling pathways, genes and treatments. This effort will help empower the generation of new disease hypotheses and connections, as well as testable predictions of potential treatments. This is an unprecedented assembly of disparate data types into a multi-dimensional relational informatics platform and will be usable by doctors, researchers and non-experts. As such, it will require extensive and complex teamwork among the scientific,

healthcare and patient communities, and we anticipate the need to use our CAN Other Transactions Authority. We expect the NCATS' matrix project to spur innovation in methods, techniques, prevention and treatments, and to help move from the "one disease at a time, one organ at a time" therapeutic model toward a far more efficient approach of studying diseases and potential interventions, including generating new hypotheses that could be tested across related diseases.

CONCLUSION

These projects are just a few examples of the exciting activities planned or already underway at NCATS. Though NCATS is still relatively new, we operate following the NCATS 3Ds: developing new approaches, technologies, resources, and models; demonstrating their usefulness; and disseminating the data, analysis and methodologies to the community. Our early successes demonstrate how this approach can help solve some of the most challenging problems in translational science. I look forward to sharing more of our achievements with you as NCATS continues to evolve.

PREPARED STATEMENT OF DR. NORA VOLKOW, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2017 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 science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health. Over the last four decades, NIDA-supported research has revolutionized our understanding of drug use and addiction, transforming our understanding of the biological, social, and environmental factors that contribute to substance use disorders (SUD), and driving the development of improved strategies to prevent and treat SUDs.

Drug use and addiction represent major public health challenges in our Nation. In 2014 alone, over 47,000 Americans died as a result of an unintentional drug overdose, and the past few years have seen rapid increases in babies born with neonatal abstinence syndrome (NAS), an unprecedented local outbreak of HIV, an increasing prevalence of hepatitis C (HCV), and new synthetic drugs flooding the market. Despite these challenges, this is a time of great opportunities for addiction research. The last few years have seen tremendous advances in technologies with research applications—from gene sequencing and manipulation, to higher resolution brain imaging technologies, to mobile health tools and electronic health records. In 2015, NIDA released an updated strategic plan focused on leveraging these recent scientific and technological advances to re-envision what research can accomplish over the next 5 years.

The NIDA Strategic Plan for 2016–2020 outlines our broad goals across basic science, prevention, treatment, and public health and identifies four priority focus areas that we believe present unique opportunities to be leveraged over the next 5 years including:⁴

1. Understanding the complex interactions of biological, behavioral, and environmental factors influencing drug use trajectories. Capitalizing on emerging technologies and discoveries to facilitate integration and analysis of diverse data sources, including genomic, behavioral, neurobiological, environmental, and other data associated with drug use and addiction.
2. Accelerating the development of treatments for SUDs. Translating basic knowledge of the molecular pathways and brain circuits involved in SUDs to develop new therapeutics for SUDs and leveraging existing safety profiles and pharmacology data to lower development costs and shorten the timeline for obtaining FDA approval.
3. Addressing real-world complexities including comorbidities and poly-drug use. Conducting research to better understand the barriers to successful and sustainable implementation of evidence-based practices and developing implementation strategies that effectively overcome these barriers to ensure that all populations benefit from the Nation's investments in scientific discoveries.
4. Advancing bi-directional translation from basic to clinical and applied research. Fostering stronger collaborations across basic and clinical researchers

⁴ <https://www.drugabuse.gov/about-nida/2016-2020-nida-strategic-plan>.

to integrate and coordinate human and animal research on addiction across the trajectory from initiation to recovery.

CURRENT RESEARCH HIGHLIGHTS

Within the strategic priorities discussed above, NIDA research is addressing ongoing national public health priorities including the epidemic of opioid overdoses, the impact of adolescent drug use on brain development, and the impact of tobacco use on health.

Addressing the Opioid Overdose Epidemic.—In 2015, both President Obama and the Secretary of the Department of Health and Human Services launched initiatives to address the complex problem of prescription opioid and heroin abuse in this country. Both initiatives are focused on improving opioid prescribing practices, expanding dissemination of the opioid overdose reversal drug naloxone, and increasing access to medication assisted treatment (MAT) to treat opioid use disorders. NIDA-supported research contributes to both opioid initiatives through support for research on alternative treatments for pain with reduced potential for abuse; treatment of opioid use disorder; and development of lay-friendly naloxone formulations.

Development of alternative pain treatments with reduced abuse potential. While many strategies are currently being utilized to reverse the opioid overdose epidemic, there remains a pressing need to develop more effective treatments for chronic pain with reduced abuse potential. NIDA, in partnership with the NIH Pain Consortium, funds research to foster development of new pain treatments with reduced potential for abuse. Funded grants range from neurobiology, genetics/epigenetics, and molecular biology research that drives early stage drug target discovery, to therapeutics development including preclinical safety and efficacy testing and early phase human trials, to health services research. For example, NIDA research is supporting:

- Testing of new compounds that exhibit novel properties as a result of their combined activity on two different opioid receptors (i.e., mu and delta). Preclinical animal studies show that these compounds can induce strong analgesia without producing tolerance or dependence.
- Development of new non-opioid medications for severe pain including compounds that work through the endocannabinoid system and others that modulate members of the transient receptor potential (TRP) ion channel family.
- Exploration of combinatorial approaches that utilize both opioid and non-opioid systems to minimize the dose of opioids needed for pain control.
- Development of non-pharmacological strategies for pain treatment including transcranial magnetic and direct current stimulation of the brain, electrical deep brain stimulation, peripheral nerve stimulation, stem cell transplants, and integrative health approaches that consider the biopsychosocial nature of pain.

Improving Treatment of Opioid Use Disorders.—An estimated 1.9 million people in the United States suffered from SUDs related to prescription opioid pain medicines in 2014, and 586,000 suffered from a heroin use disorder. Despite the availability of evidence-based pharmacotherapies for opioid use disorders, including methadone, buprenorphine, and extended-release naltrexone, we have a significant and ongoing treatment gap in our Nation with more than a million persons unable to access care and less than 40 percent of those being treated for opioid addiction receiving these medications. NIDA supports a broad portfolio of research to improve treatments for opioid use disorders (OUDs) ranging from basic research to identify novel targets for new therapeutics to preclinical and early clinical trials of new or improved therapeutics; to implementation science to improve the dissemination and effective use of evidence based practices.

For example, NIDA research supported the development of a buprenorphine implant (Probuphine), a novel formulation that provides stable round-the-clock dosing for 6 months. Buprenorphine is one of three FDA approved medications that has been shown to be a safe and highly effective treatment for opioid addiction. This new formulation delivers a steady dose of buprenorphine for 6 months, an innovation that improves the efficacy and acceptance of buprenorphine maintenance treatment by: 1) removing the need to take a daily pill, promoting continuous patient adherence; 2) preventing diversion of the drug; and 3) eliminating the risk of accidental ingestion by children. FDA accepted a resubmission of the Probuphine New Drug Application (NDA) that includes results from a Phase III double-blind clinical study in September of 2015. Agency action is expected by May 27, 2016.

Development of Lay-Friendly Formulations of Naloxone.—The opioid overdose-reversal drug naloxone can rapidly restore normal respiration to a person who has stopped breathing as a result of overdose from heroin or prescription opioids. Naloxone is widely used by emergency medical personnel and some first responders and a growing number of communities have established overdose education and

naloxone distribution programs that issue naloxone directly to opioid users and potential bystanders. As of 2014, more than 152,000 naloxone kits had been distributed to laypersons, and more than 26,000 overdoses had been reversed since 1996.

In late 2015, FDA approved a user-friendly intranasal formulation that was developed through a NIDA partnership with Lightlake Therapeutics, Inc. (a partner of Adapt Pharma Limited). This formulation can easily be used by potential bystanders (laypeople) and is an important advance beyond the improvised nasal devices (consisting of a syringe of injectable naloxone attached to an atomizer) that have been used in recent years.

NIDA also continues to support implementation science to develop strategies to improve the dissemination and sustainable implementation of naloxone distribution programs; to increase co-prescribing of naloxone to patients receiving opioid medications; to test strategies for teaching high risk individuals strategies for managing overdose and mitigating risk; and to test the efficacy of pharmacy based naloxone access policies.

Basic Research on Brain Development and Drug Use Trajectories.—NIDA supports a robust portfolio of basic research to understand the mechanisms that underlie the transition from drug use to addiction and the brain changes that characterize SUDs. One illustrative example of this type of research is the Adolescent Brain Cognitive Development (ABCD) study, a landmark study led by NIDA in partnership with NIAAA, NCI, and other NIH partners that officially got underway in September 2015 with 13 grants. Researchers will recruit approximately 10,000 children at age 9 or 10—before initiation of drug use—and collect detailed neuroimaging, genetic, behavioral, environmental, and other health data at periodic intervals over the course of a decade. This study will examine how biology and environment (including drug use) interact and relate to developmental outcomes such as physical health, mental health, and life achievements including academic success. This study will allow us to answer questions such as how does marijuana use during adolescence affect the development of the human brain and how does this subsequently influence behavior. Such information is crucial to guide prevention efforts.

Research on Tobacco Use and Health.—Smoking is the leading preventable cause of disease, disability, and death in the United States. Over 480,000 Americans die each year from smoking and second hand smoke exposure. NIDA partners with FDA's Center for Tobacco Products on the Tobacco Regulatory Science Program (TRSP) to support research on the impact of tobacco-related policies on population health and on the Population Assessment of Tobacco and Health (PATH) Study, a national longitudinal study of tobacco use and how it affects the health of people in the United States. One recent study evaluated the effects of smoking cigarettes that contained different levels of nicotine among current smokers and found that the average number of cigarettes smoked per day was lower after six-weeks in participants randomly assigned to cigarettes containing lower amounts of nicotine. Compared with the normal (control) cigarettes, the cigarettes with lower levels of nicotine decreased exposure to and dependence on nicotine and also reduced craving during abstinence from smoking.

Ongoing studies are examining how low-nicotine cigarettes affect smoking behavior in vulnerable populations including women of childbearing age or pregnant women, individuals with comorbid SUDs, and individuals with comorbid serious mental illness. Each of these populations is at increased risk for tobacco use and dependence or tobacco related adverse health outcomes. Yet despite these serious vulnerabilities, these populations have not typically been included in tobacco regulatory studies.

CONCLUSION

Drug use and addiction are complex conditions. The fiscal year 2017 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 to advance prevention and treatment and improve public health.

Senator BLUNT. Thank you, Dr. Collins. We're on a pretty tight 5-minute clock here on questions. If anybody wants to stay—I'm sure there will be a time for it—and can stay, there will be time for a second round of questions.

RESEARCH BUDGET CUTS

Dr. Collins, what would happen if we cut your research budget by \$1 billion, as the administration's request asked us to do?

Dr. COLLINS. Losing \$1 billion for medical research at the present time would be devastating. We would have to cut the number of new and competing grants that we give by a very substantial number. Great ideas that scientists are putting forward would go unsupported. Momentum that has been started thanks to your efforts in fiscal year 2016 would be severely damaged as a result.

MANDATORY FUNDING

Senator BLUNT. Do you know something I don't know that would suggest that the mandatory funding at a level that exceeds that is likely?

Dr. COLLINS. Well, Senator, I have to say when it comes to the discussions about discretionary budgets versus mandatory budgets, I think all of us at NIH are a little puzzled by exactly what the consequences of those particular options might be. Our concern is to try to see, by some means, an increase in the support for biomedical research at a time of such great opportunity. So I'm not sure I can weigh the balance, but it would certainly be, as a bottom line, deeply unfortunate if these kinds of conversations resulted in an overall decrease in the resources that we have when we have been hoping very much, as you and others have projected, that perhaps we are finally turning a corner after 10 years of lost resources into a positive space, as happened in 2016 and as we very much hope can continue in 2017.

YOUNG RESEARCHERS

Senator BLUNT. And one of the things we had hoped we would achieve from conversations we've had with all of you in the past would be encouragement of young researchers. I know you just now have this 6.6 percent increase, the \$2 billion increase. It may be too early to project, but do you want to create a sense for us of what you're seeing in the research community generally and young researchers specifically?

Dr. COLLINS. Thanks for that question because it's looking certainly much more encouraging than if you had asked me that question 2 or 3 years ago. Just a couple days ago, I was at a major meeting of the basic scientists called ASBMB in San Diego, and I spent a lot of time talking to young researchers. A couple of years ago, those conversations were pretty difficult, our young researchers wondering if they had a career path, wondering if there was going to be support for their ideas. It feels different this year. They have gotten the sense that there is a path here for their careers, that they can try innovative ideas and expect that there is going to be a possibility of living out those kinds of career dreams.

And we're all about supporting them, and we have taken a number of measures to try to achieve that kind of support. For instance, early-stage investigators, who are not as experienced as the more seasoned ones, compete against each other instead of against the seasoned investigators in our peer review, and that gives them a bit of a boost.

We started a whole new program that I am personally very attached to, which allows the most talented graduate students to skip the postdoc all together and go straight into an independent position because we know that a lot of the great ideas that scientists have don't happen when you're 50 or 60, they happen at a little earlier stage than that, and yet we have oftentimes kept people in less than fully independent positions for a long time.

Something that's recently been floated, and I think may very well come through in terms of a way of attracting more physicians particularly into science is our loan repayment program, where we try to counter what is otherwise a major financial hit for those who have big medical school debts and want to go into research. And you have recently proposed in the authorizing side of this an increase of the loan repayment program to a higher cap of \$50,000 instead of \$35,000 and that will improve, I think, our opportunity to recruit those much needed researchers into our workforce.

So many different points here we're trying to push simultaneously. The most important thing, though, is for the overall tide to raise and lift all those boats, many of them with young investigators in them with their dreams of doing great things, but dependent upon a confidence that we're on a stable, positive trajectory for research that will go over many years and not have a feast or a famine.

Senator BLUNT. In this budget year we're in right now, if I understood this right, you hope to set aside a certain amount of research dollars for young researchers specifically and then they would be competing against other young researchers. Do you have a sense of how big that amount of money might be?

Dr. COLLINS. So we're dependent on, of course, what comes in as far as applications. What we are making sure is that those new and early-stage investigators have a chance to compete against each other, and that gives them a boost in the priority scores. And, in fact, in recent years, something like 35 percent, if I remember correctly, of our grant funds go to new and early-stage investigators. They're not all young scientists. Some of them are scientists who have been working in other fields like engineering or physics or mathematics who now see biology as a place that they would like to come and do their work, but we want them, too, and we want to be sure they have a fair shake at getting started on their careers in our particular community.

Senator BLUNT. Now, we may come back to engineers later and something that I saw the other day at the Thompson Center for Autism at the University of Missouri, but I'm going to try to keep my time with everybody else's.

Senator Murray.

COLLABORATION IN ALZHEIMER'S RESEARCH

Senator MURRAY. Thank you very much.

The Vice President's Moonshot Initiative has actually increased awareness about some of the barriers to sharing data among cancer researchers, and I understand there's been some success at fostering greater sharing of research data among those focused on Alzheimer's disease with a range of formal public, private, State, and Federal international cooperation. Can you share with us a lit-

tle bit about how NIH has been able to foster this better collaboration and the effect it is having on our efforts to develop treatments and ultimately a cure for Alzheimer's and related dementia?

Dr. COLLINS. So I appreciate the question because this is something we're very intensely focused on, is the idea of data sharing. And NIH is pulling all the levers that we have and are happy for others that maybe get granted to us to be able to insist upon that. Let me ask Dr. Hodes, who is overseeing this for Alzheimer's, to respond to your question.

Dr. HODES. The microphone is on? Yes. Thank you very much for the question, and it touches upon a very important aspect of progress to success that I think reflects the understanding from public—or private sector about common purpose and the advantage of working together to ultimately accomplish the common goals of finding diagnostic and therapeutic interventions.

So to be specific, I can cite one of those, which Francis Collins initiated NIH-wide, the AMP, or Accelerating Medicines Partnership. It's a great example. One of the diseases being approached in this sense is Alzheimer's disease. It brings together contributions from pharma, from biotech, from advocacy and philanthropies, along with NIH dollars, and in this case, for example, in two general areas. One of them supporting in clinical trials the use of new biomarkers; the other, looking at the grand progress in "omics," proteomics, genomics, metabolomics, looking at the differences in the brains of people affected by Alzheimer's and those not. These data now are integrated in near real time through a common database. It's a new culture among investigators in the academic sense, as well as with industry to make the data, the products of research, available as quickly as possible to the community, as posted, and we'll have enormous repercussions, I think, in accelerating the progress of research. And again this idea reflects a common purpose in understanding that it would benefit everyone, ultimately product development, and there's a way to achieve that, expansion in basic science and knowledge. So it has been an enormous success. I think it's a culture change that will perpetuate.

ALZHEIMER'S DISEASE FOR AT-RISK POPULATIONS

Senator MURRAY. Good. And I think part of that, from what I'm hearing, is that instead of waiting till someone is older and in further stages of Alzheimer's, you're looking at ways to have new trials with participants who are at risk of the disease rather than already being diagnosed?

Dr. HODES. Exactly true. One of the advances we've seen, by understanding of genetic determination of those at risk and by biomarkers, notably neuroimaging, is the ability to detect early stages of Alzheimer's, related dementias, long before the appearance of symptoms, and now to design treatments to intervene and allow us to monitor these biomarkers to see if we're engaging the right targets, having signs of progress, and therefore identify successes, and for that matter, failures more quickly and have an opportunity to test more candidate interventions.

BIG DATA TO KNOWLEDGE

Senator MURRAY. Okay. Very good. We hear a lot about big data challenges facing researchers, and perhaps nowhere is that more relevant than with the massive amounts of data that the BRAIN Initiative is now generating, a challenge that's only going to increase, I assume, as we learn more. I know some of your team has been really focused on this, and I wanted to ask you about the challenge of opening and integrating an accessible data warehouse on a massive scale and maybe some of the examples you've seen that you've learned from.

Dr. COLLINS. So we do in fact have major investments in the space of big data. I just showed up on this screen, there are all kinds of data types that are being generated now in very rapid phase and produce very large datasets of terabytes. And you mentioned the BRAIN Initiative as an example. Genomics is certainly in there as well as imaging.

And now with electronic health records becoming accessible for research purposes, NIH recognizing this was going to be a major need and a potential threat if not attended to, put together a plan which has now resulted in \$100 million of spending on a program called BD2K, Big Data To Knowledge, which aims to try to take all these large datasets, develop the appropriate ways to have standards so that they can be properly compared and integrated, and develop new kinds of software to mine the nuggets of information out of these very complicated sets. This supports a number of centers of excellence in data science around the country and also it is the major source now of training for the next generation of data scientists, who we are going to need to be able to handle what is clearly a growing area of scientific opportunity and responsibility.

Senator MURRAY. Okay. Thank you.

Senator BLUNT. I would normally go to Chairman Cochran, but he says he was a little late getting across the street, so he didn't want to get in front of anybody who was already here.

And Senator Alexander, you're the first person who was here.

Senator ALEXANDER. Thank you, Senator Blunt.

Senator Cochran, thank you.

Welcome, Dr. Collins, and your team. I want to first express my appreciation to Senator Blunt and Senator Murray for their leadership last year on the significant increase in funding for the National Institutes of Health, which I am glad to support. I don't think there's anybody here who doesn't hope that we can find ways to make the increase that happened last year a pattern this year and in the future. So I thank Senators Blunt and Murray for their leadership on that in this committee.

Second, thank you for mentioning the work that our authorization committee has done. Senator Murray is ranking on that. We finished our work in the committee. We've done the things that you have asked us to do. You said the ability to recruit top talent was very important for you. We've made many of the changes you suggested. Electronic medical records are absolutely essential to the Precision Medicine Initiative you described. We've done a number of things there.

The Vice President is talking about making researchers who use NIH funds share their data. You've talked about that. That's in the bill that we passed yesterday.

Dr. COLLINS. Thank you.

Senator ALEXANDER. We gave you more flexibility to make alliances like the Google-Vanderbilt alliance that the President announced not long ago. We reduced a number of really pretty silly provisions that create a lot of unnecessary paperwork. So we asked you, what could we do to create an environment where you could succeed? And we tried to do that.

Now, the major thing remaining is what I would describe as an NIH innovation project fund and how to pay for it. The House of Representatives has already passed its 21st Century Cures Act. They appropriated \$8.8 billion in mandatory funding. I've tried to come up with a way to do that in the Senate. We can reduce existing mandatory spending to pay for the NIH innovation projects fund, we would make sure that we have appropriate oversight, and it would not replace increases in annual discretionary funding.

MANDATORY FUNDING FLEXIBILITY

So let me ask you in the remaining time to comment on that. Are the priorities that I suggested earlier, launching Precision Medicine, Cancer Moonshot, the BRAIN Initiative, 650 American young investigator corps, big BioThink awards, are those still priorities? Can you do those without creating funding cliffs? Would mandatory funding somehow give you more flexibility to ramp spending up and then down? And what would you do about oversight in terms of a strategic plan for each of those five areas?

Dr. COLLINS. Well, thank you for that question and your leadership, Senator. We are enormously excited about the five areas that you just enumerated, the focus, for instance, on young investigators trying to create an even more vigorous pathway for their recruitment and support, which is one of those five; the big BioThink, which you mentioned, which is an opportunity for all of the 27 Institutes to have a chance to put a challenge out there to their community about what are the really big ideas that could go forward in the next few years. And, of course, Precision Medicine and the Cancer Moonshot and the BRAIN, all very high priorities for us.

While I totally agree with what you said about the importance of not having this kind of mandatory funds displace regular discretionary support, because that would be a very unfortunate outcome, we do believe that for those five areas, we could, in the space of a few years, identify components that could be nicely supported through this mechanism and would not result in a cliff, and which would, if we were given appropriate flexibility, be something that we could put forward in terms of what those timetables would look like and what those envelopes might look like as far as specific dollar figures.

And I certainly agree that we would expect to have appropriate oversight about how those dollars would be spent. We would be happy, in fact, to submit a work plan and then be held accountable for that over the course of the coming years to make it very clear that we do understand this is a big responsibility that you, through

the congressional process and speaking for the taxpayers, expect us to use and——

Senator ALEXANDER. So you do believe that in those five areas those are still priorities that you've identified——

Dr. COLLINS. Absolutely.

Senator ALEXANDER [continuing]. And, second, that you could identify elements of them that would be discrete, have a beginning and an end, do them without creating a cliff, and perhaps even the mandatory funding would provide us a way to give the NIH funding in a way that you didn't have to spend it all at once and you could ramp up and ramp down according to the real needs of the project.

Dr. COLLINS. That's exactly right. Yes, I do believe these are major priorities. We could design things that way, and I appreciate what you said at the end about the flexibility that would help us a lot in terms of designing the exact funding envelope that would make the most sense for each of those five programs.

Senator ALEXANDER. Thank you, Mr. Chairman.

Senator BLUNT. Thank you, Senator Alexander.

Senator Durbin.

NIH MARCH-IN RIGHTS

Senator DURBIN. Thanks very much, Mr. Chairman.

And thank you, Dr. Collins, for being here with your team. It's a moment of satisfaction and pride that we look at this year's budget and contemplate next year's budget. Though I am a strong supporter of my President, I do disagree with their budget request and believe that we can do better. The encouraging thing is that gathered at this table on this side are men and women who have proven that in this fiscal year and can prove it again. It's going to take some good luck, but we have some exceptional leadership here, not only in terms of Senator Blunt and Senator Murray on this subcommittee, but Senator Alexander and Senator Murray working on the authorizing committee, and not to overlook at all my close friend and colleague, Senator Cochran, who has overall responsibility for the Appropriations Committee. So among us is the opportunity and the potential to meet this year's challenge and next year's budget, and I hope that we can do it.

I would like, if I can, to move to an area separate, but I think very important, when it comes to the medical health of America. A recent Reuters report found that the prices of four of our Nation's top 10 drugs have increased more than 100 percent since 2011; 6 others went up 50 percent. The price for arthritis drug Humira went up 126 percent; multiple sclerosis drug Copaxone, 118 percent; asthma drug Advair, 67 percent. The list goes on and on.

What makes this so worrisome is not only it limits accessibility for the American people, but it also is objectionable because many of these drugs were developed at the expense of taxpayers, taxpayers funding the National Institutes of Health. These taxpayers have paid to develop drugs that they now cannot afford, while drug companies make record profits.

The National Institutes of Health has historically been reluctant to exercise march-in rights, an existing authority that was created

by the Bayh-Dole Act that allows the NIH to grant a license for others to use drugs developed with NIH dollars which are inaccessible to those in need. I agree that we need to be especially careful in this area of intellectual property protection and that march-in rights have to be used sparingly, if at all. But when we take a look at the staggering prices of drugs, the dramatic increases for drugs, many of which have been on the market for years before these increases took place, I ask you, have you considered, would you consider, using your statutory authority under the Bayh-Dole Act for march-in rights to protect the consumers of America from abuse by overpricing by pharmaceutical companies?

Dr. COLLINS. Senator, I share your concern about the way in which individuals who need access to medical treatment may be prevented from readily achieving that on the basis of the costs involved, and certainly, as a physician, I would never want to see a circumstance where an effective drug was not available to somebody who needed it and would benefit from it. But I'm not sure that NIH is in a great position here in terms of the levers that need to be pulled to try to do something about what everybody agrees is a difficult situation with drug pricing.

The Bayh-Dole Act, which I recently went back and looked at in terms of those march-in rights and what they were intended for, does not appear to have really been designed to be utilized in a fashion where the price is the obstacle, it seems more to be a circumstance where the product was simply not available because it was not being commercialized, and then NIH had the authority to step in and take over. And, of course, it only applies if NIH has some connection to the intellectual property, which is true for many drugs, but certainly not all.

We are certainly looking at the situations on a case-by-case basis. We have a recent letter from a few Senators about something called Xtandi, which we're studying at the moment, and I am not saying in any way that we're not going to take this potential responsibility seriously, but I am concerned the negatives that may be flowing forward. If we begin to use march-in in a very broad way about drug pricing, it may in fact be substantial in terms of a loss of interest then in terms of industry participation in discoveries that NIH has supported.

ACCESSIBILITY OF DRUGS

Senator DURBIN. Let me just, because my time is up here, let me just say first, accessibility I think goes beyond physical accessibility. If a drug is overpriced, it is not accessible to a consumer. And, secondly, I accept your premise that you don't want to abuse this right, but if you cannot find one egregious example where you can apply this, I would be surprised. And applying it even in one case sends at least the message to the pharmaceutical companies across America that patients need to have access to drugs that were developed with taxpayers' expense and the research that went into it. I think doing nothing sends the opposite message, that it's fair game, open season, for whatever price increases they wish.

Senator BLUNT. Senator Cassidy, and after that it will be Senator Mikulski.

Senator Cassidy.

Senator CASSIDY. Thank you. Dr. Collins, all of you, thank you very much. Thank you for your service to our country.

Dr. Collins, first I want to thank you. We've spoken in the past. You know, I've kind of made it my jihad to get NIH to redirect dollars to more pressing current biomedical needs. You've initiated that, and I thank you for that, and I look forward to seeing the fruits of that, because I look up and down the panel, you all have got a lot of work to do, and we thank you, too.

PRECISION MEDICINE INITIATIVE RECRUITMENT

Secondly, I've been thinking about your Precision Medicine Initiative. What is the business plan? There's a million people that you wish to recruit, it supposed to reflect the diversity of our country. I've done clinical research, nothing like you all, but significant, and my patient population was lower income, more transient lifestyles. We successfully recruited, but this would be for a 6-month or a year study, nothing such as ongoing for the rest of their life.

Dr. COLLINS. Right.

Senator CASSIDY. So in your business plan, I have several questions. You have an ambitious effort to recruit a million people from all socioeconomic groups. How do you plan to do so? Secondly, it's longitudinal. There is going to be significant expense. So to what degree do private entities, say, Pfizer, do they have to pay to access that data? If not, why not? Because there are going to be significant benefits.

And, thirdly, if I am someone who has agreed for the rest of my life to contribute hair and rectal swabs and nasal swabs and everything, because you've spoken of our biome being included as well as our genome, am I going to get to share that? If there are a billion dollars that come in, in revenue, a certain portion ideally would be used to maintain the program, does some of it flow back to one of those million? We think of that HeLa strain, the woman who donated her cervical cancer, so much benefit, but her family has not benefited directly.

Dr. COLLINS. Not directly.

Senator CASSIDY. In this contractual process, will those who contribute their data, will they be able to benefit as well?

So it's three questions, if you will.

Dr. COLLINS. Well, thanks for the question and also for your initial comment about strategic planning. I hope everybody at the dais there has seen the strategic plan that NIH put forward, published in December, very much a response to your request to have a clear sense of how we set priorities, and I hope you've had a chance to look at that, and if not, please do, and let us know if there are things you would like to discuss further about it.

How are we going to enroll a million people and have that be generalizable as far as the population in the United States? Something we've thought about a great deal. Many of the participants are in fact going to be those who are currently involved in health provider organizations who have recently come forward and applied to be part of this, but, of course, that's not going to be fully diverse in terms of socioeconomic and ethnicity of the country.

We will also have an outreach which is, I think, going to be pretty interesting to the community health centers, the federally Quali-

fied Health Centers that are supported by HRSA (Health Resources Services Administration), to try to enroll those individuals who get their care in those settings, who tend to be fairly stable in terms of their geographic location, despite what people might think. And actually I have interesting research based on polls, but haven't generally been asked.

We also will have this open to any American, so anybody can volunteer to take part in this, and that opportunity will appear at approximately August or September. So maybe all of you all would like to join in. It would be great to have you as members of this million-strong cohort.

Yes, it is intended to be a longitudinal cohort. It will collect a great deal of data. We do intend to make that data available to any qualified researcher who adheres to certain principles about protecting the privacy and confidentiality.

I hear what you're saying about pharma therefore being able to use this as well, and yet I don't see a great alternative. Basically, pharma will have the opportunity to learn from this. It will be very pre-competitive, early-stage data, the kind that we traditionally do make available in publications, and it would be hard to put up a barrier here, I think, in this case, without slowing down the progress of research overall.

Finally, your question about whether the participants should receive some of the financial benefits that may come out of this, we've certainly talked about that. I think the general position, though, of bioethicists who look at that question is that the extremely low likelihood of such actual benefit coming back because the data that we generate here is not itself likely to produce much in the way of intellectual property, it's pre-competitive data, it might actually be a disservice then to be seen by potential participants as an inducement to take part in a project which might not really result—

COMPENSATION FOR PMI COHORT PARTICIPANTS

Senator CASSIDY. If I may, I know in clinical research, you're allowed to compensate people for the expense of participation.

Dr. COLLINS. Yes.

Senator CASSIDY. So it isn't an inducement as in, you know, stick a nail in your eye; it is, listen, you're going to be taking your hair, you're going to put it in an envelope, you're going to mail it to us, you're going to give us access, a lot of hassle associated with that. It is a compensation for participation.

Dr. COLLINS. So we would certainly be willing and have it planned to compensate people for the time that they have to spend by taking part in this, if they're going to have an examination, have a blood sample, have to—

Senator CASSIDY. In my remaining seconds, let me interrupt. Now, the thing that concerns me regarding this data, granted, it's pre-competitive, but we, as taxpayers, funded for electronic medical records to collect this data to make it generalizably available to people doing public health. We heard when I was in the House on Energy and Commerce, it's not being used that way. Insurance companies are instead packaging and selling to big pharma, but \$500,000 for a cohort of information, and if you are a dadgum pub-

lic health doctor and you don't throw in \$500,000, you don't get the data.

So I guess my concern is the taxpayers investing heavily in this, but our precedent is, is that the taxpayer is misled in terms of its generalizable use. For this data, there is going to be such profit generated, is there really no way that the person that comes up with a blockbuster drug in any way comes back to help support the maintenance of this dataset, which is going to be critical to their development of that blockbuster drug?

Senator BLUNT. Can you respond to that in 30 seconds, Dr. Collins?

[Laughter.]

Dr. COLLINS. Sure. I guess, Senator, I see this as not so different than the way in which our American ecosystem has flourished, and I would be reluctant to try to impose that kind of payback provision for pharmaceutical companies to be able to get access to a very large dataset which is pre-competitive which may give them ideas about new drug targets they hadn't thought of, but which is probably not going to result in a direct intellectual property claim. So I think of this much more the same way that the Framingham Study has produced all kinds of insights about heart disease, and nobody has contemplated that the companies that are selling statins should now be paying money back to Framingham.

Senator BLUNT. Thank you very much. There will be time to come back to that and other topics, as we all want to as well, Senator Cassidy.

Senator Mikulski.

Senator MIKULSKI. Mr. Chairman, thank you.

Senator Murray.

Dr. Collins, it's so good to see you and your team here and those also who represent institutes and offices at NIH. You know, this might be your last hearing, but it certainly is my last hearing at the appropriations for NIH, but I'll be out there on Monday to be able to talk to you on more detail.

It has been my great joy, one of the greatest joys I've had being in the Senate, was to be able to represent the National Institutes of Health, both my work in the House on Energy and Commerce, where so many of us came from, to now certainly in the Senate, and to represent both NIH in the Bethesda campus, our two institutes in Maryland, the one on Aging and on Drug Abuse, and of course, our extramural work with Johns Hopkins, the University of Maryland, and multiple campuses, one of your rival institutes, the Craig Venter, where we watched you and Dr. Venter do the race to map the human genome. So it has been a great joy. It will be even more joy if I can help leave you in pretty solid financial health. We could go through the numbers about clinical trials and so on, but let me tell you my principles and then get to my questions.

Number one, do no harm. So either for this year or next year, that through our own self-inflicted wounds, we're ready to budget processes of sequester or shutdown, we don't go in that direction. I really want to compliment Senator Cochran and Senator McConnell and say we're going to follow regular order and do our job. So one, do no harm.

Second, capitalize existing programs. So those that are already on their way, that we help sustain so that the researchers, both senior researchers and the new ones we hope, and so on, have predictability.

And then third, go for the big ideas.

BASELINE FOR FUTURE YEAR BUDGETS

So let me then get to my question, which goes to we have an agreement here to do no harm, and I really look forward to working with my colleagues on my side of the aisle to move our process forward.

But let's go to the money. You answered Senator Alexander in terms of mandatory funding. I'm squeamish about mandatory funding. I am concerned that it is a hope and a promise. It rests on new revenue. Well, maybe. I'm coming back to actual discretionary funding, so no matter what, you, as the administrator and the director of the Institutes, because we don't earmark, we've never earmarked at NIH, though there's been a tendency, yet discretionary.

So you have a request for here it's \$33 billion, but in terms of real discretionary money, what is it that NIH needs to be able to be and do the job it wants for the next fiscal year and make sure we have the baseline to build on it, you know, on future years? Because you, research, researchers, need predictability over multiple years.

Dr. COLLINS. Senator, I can't say enough how much I've appreciated your support over these years, just a remarkable leader, and we look forward to celebrating you next Monday when you come out to NIH.

Senator MIKULSKI. The golden Petri dish, I guess.

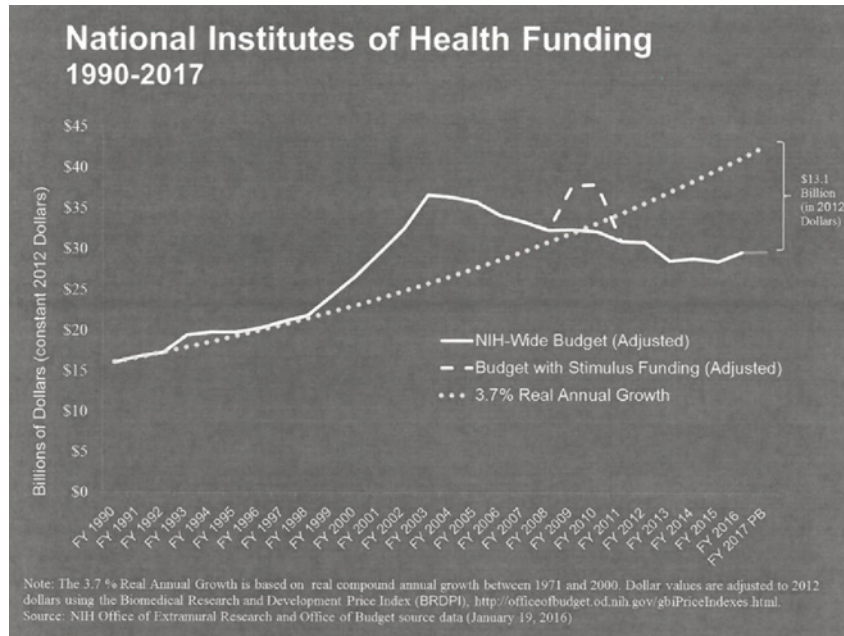
[Laughter.]

Dr. COLLINS. So in terms of your question, and I assume you're asking for my professional judgment, which I'm always happy to be asked about.

Senator MIKULSKI. Yes.

Dr. COLLINS. We have, of course, seen over the course of the last 12 years a pretty tough period for NIH until this year, fiscal year 2016. I've often thought it was useful to show this graphically, and if you look at the screen——

[The graphic follows:]



Senator MIKULSKI. I need a short answer so I can get to other questions.

Dr. COLLINS. Okay.

Senator MIKULSKI. Okay?

Dr. COLLINS. You can see the white line. That's what's happened to our resources over the course of the last 20 years, and we have made some progress this year, but we need—

Senator MIKULSKI. The number now. This is not a colloquium; it's a hearing, please. How much do you need?

Dr. COLLINS. A stable trajectory of inflation plus 5 percent for multiple years in a row would be a wonderful way to support medical research in the way that it needs to be.

Senator MIKULSKI. So if we made that percentage—now, wouldn't that be over a 5-year period, wouldn't we get to almost doubling NIH?

Dr. COLLINS. You would get to doubling by about I think 7 years or maybe 8. I would have to go back and do the compounding again, but about that.

Senator MIKULSKI. Well, first of all, I'm so pleased last year at the splendid bipartisan way we worked together, and I want to compliment Senators Blunt and Murray in doing that. I think we need to really be serious about thinking about that as a model to be able to have the predictability, again not a guarantee, we don't know what lies ahead in some instances for our country, but I think that type of commitment, along with maybe the hope and promise of mandatory funding, would be the way to go.

Dr. COLLINS. Okay.

RESEARCH IN EXISTING PROGRAMS

Senator MIKULSKI. Now, let's go to what we would buy for the money, what we would get for the money. First of all, I support these new ideas, and you know, Precision Medicine, the BRAIN Initiative, and all of this promise, but where do you see in terms of existing programs where you see some of the greatest promise? Yes, we're working at the BRAIN, et cetera, but what about things where people are often the sickest the most with awful consequences, diabetes and heart disease?

Dr. COLLINS. Great promise in diabetes, heart disease. Cancer is at a unique moment. Conditions like autism coming forward. Vaccines, the opportunity to prevent diseases that we desperately need to get on top of, like Zika and others. But, you know, the good news is if you look across the entire landscape of NIH research, there's not really a sort of place where things are in a cul-de-sac. All of those areas, and that includes the basic science agenda that undergirds it all, are poised for dramatic advances. So it's almost hard for me to pick one or two.

I do have to mention Alzheimer's. I think we are at a inflection point for that condition, and I know that's one you've had major leadership in trying to draw to people's attention. The ability now to be able to identify who's at high risk and conduct these trials to reduce their likelihood of developing the disease is looking more promising than ever.

Senator MIKULSKI. Well, my time is up, but in the area of Alzheimer's, I remember when Senator Bond and I had a hearing and we were in the poise of breakthroughs. So that was like 5 years ago. So we're always poised during the breakthrough, and I'm ready for the breakthrough.

[Laughter.]

Dr. COLLINS. So are we.

Senator MIKULSKI. So let's all continue to work together.

Thank you. You were indulgent with the time.

Senator BLUNT. Thank you, Senator Mikulski, and thank you for how well you've represented NIH as a Senator and as their advocate for a long time now.

Senator Capito.

OPIOID ABUSE

Senator CAPITO. Thank you, Mr. Chairman. And thank all of you, and thank the ranking member.

I'd like to talk with Dr. Volkow about the National Institute on Drug Abuse. As you probably are aware, I represent the State of West Virginia. We've been particularly hard hit by the epidemic of opioid abuse in the country. And I just had a few questions I wanted to ask specific to that.

I understand that you are partnering with the Appalachian Regional Commission to improve opioid intervention services. Can you explain and tell me what are the goals of this collaboration and where you are on that?

Dr. VOLKOW. We're trying to actually create infrastructure that will allow us to launch research projects and also to give us information about the nature of the problems that they currently have

vis-à-vis injection drug abuse and the associated consequences along with medical infrastructure that they have that they could deploy. Unfortunately, this information is currently not available and there are not integrated groups that would allow us to deploy the type of implementation research that we would be very much interested to do in order to contain the injection drug abuse epidemic in that area.

Senator CAPITO. Well, I understand there have been issues with different States on reporting data, causes of death, and because there are associated issues, it could be a heart attack, and then not be identified as a drug overdose. Is this an issue across the country? I'm sure it is.

Dr. VOLKOW. Yes, it is an issue, and as a result of that, we don't have clear-cut numbers of the cases that is related to opioid overdoses, and varies, as you said, by State.

Senator CAPITO. So I'm sure, as a researcher, you don't want to speculate, but I would imagine speculation is the problem. It may be greater than what we really realize according to the data?

Dr. VOLKOW. Yeah, there is consensus that we are underestimating the numbers that's associated with—

Senator CAPITO. Well, that's a frightening thing I'm sure for you all and certainly for all of us, every family that's affected.

DEVELOPING NON-ADDICTIVE PAIN MEDICATION

I was pleased to hear, Dr. Collins, in your opening remarks, that you talked about the research that's being developed to find a non-addictive pain medicine. I know Secretary Burwell has talked about this as well. How far along are we on that and what can we expect there? If you could just shine a little light on that.

Dr. COLLINS. Sure. I might ask Dr. Koroshetz, who directs the Pain Consortium at NIH, to say something to respond to your question.

Dr. KOROSHETZ. Yes. So it's an interesting area to think about. Pain is something we all have. It's good to know we have a sense of pain. But the problem that we're facing is we don't understand too well about what characterizes the transition from acute to chronic pain. Chronic pain is not helping in any fashion whatsoever. We think, and all the evidence so far, suggests that there is a change in the brain circuits that occurs after someone has been exposed to an acute pain that leads those circuits to change and develop a chronic pain disease basically by itself.

So we have pretty good information on some of the beginnings of how that happens. It starts very peripherally and moves more centrally over time. And there actually are targets for therapy that could be pursued by pharmaceutical companies and by the NIH to try to prevent that transition. So in the Blueprint for Neuroscience, that was our major challenge, to develop products that would prevent this acute-to-chronic pain transition. From talking to the pharmaceutical companies, I have a lot of leads.

I think the problem that we have to focus more on is how to improve the testability of those compounds as we go into people because we're still reliant upon someone's reporting of their pain, and we don't have objective measures. So we think at NIH that that should be our major focus. And the drug companies tell us they

have lots of targets, but they need this objective measure. So that's where our focus was.

Senator CAPITO. Well, I would hope—I mean, I'm pleased to hear that. I would like to see it on the fast track. I think for a business model, you know, there's going to be a lot of demand for a non-addictive pain medication that works.

Dr. KOROSHETZ. Right.

Senator CAPITO. So I don't see how the private sector would be contrary to this at all, and so I'm pleased to know you're working together.

NEONATAL ABSTINENCE SYNDROME

The last issue, again, Dr. Volkow, about fetal—let's see, neonatal abstinence syndrome, that's babies that are born addicted, and this is an issue, and our State has particularly high statistics here again. Are you pursuing research in this area or what kind of partnerships are you doing here to try to help those very innocent victims of drug abuse?

Dr. VOLKOW. Indeed, we are pursuing the area of research in terms of interventions, number one, to prevent neonatal abstinence syndrome, and number two, in those women that are opioid—have an opioid use disorder, to determine what are the best treatments that can be given to them in pregnancy to minimize the likelihood that those infants will suffer from neonatal abstinence syndrome. So we are working on prevention and on treatment.

Senator CAPITO. Well, thank you very much. We have a place in West Virginia called Lily's Place that helps to deal with these babies. And just my final comment would be I noticed in your report that you're working on a Human Placenta Project. I'm very interested in that and have a personal connection with that. So thank you very much.

Senator BLUNT. Senator Schatz.

Senator SCHATZ. Thank you, Mr. Chairman.

Thank you to all of you and everybody who works at the National Institutes of Health. This is, I think it's fair to say, among the most inspiring, invigorating hearings that we have. I'm going to try to get to a couple or maybe three questions.

FEDERAL PAIN RESEARCH STRATEGY

First, Dr. Volkow, following up on Senator Capito's question about non-addictive alternatives to the current pain medication, opioids, acetaminophen, the NSAIDs, where are we with that in terms of the national—the NIH is working on a Federal pain research strategy. When will this be completed? And when will it be launched? And who is going to be point on this? And I'm not sure if the question should be directed to Dr. Volkow or Dr. Koroshetz.

Dr. COLLINS. Koroshetz will answer.

Dr. KOROSHETZ. It's really complicated. There are a bunch of different documents out there, but there is a National Pain Strategy that has been released, and that is basically directing the country's medical care system on how to improve pain care in both a safe and effective manner. And then that process is followed by the Federal Pain Research Strategy, which is being developed now and will be completed by January 2017, where an expert panel of basic and

clinical researchers will work out the highest research priorities in these different areas, some of which I mentioned, the acute-to-chronic pain transition being one. And another what is determining the best way of treating people who have chronic pain, depending on what caused it and what type of pain it is.

Senator SCHATZ. Great. Thank you.

PUBLIC HEALTH STRATEGIES FOR DENGUE/ZIKA

Dr. Collins, as you know, the Hawaii Islands, the State of Hawaii, but the big Island of Hawaii, is experiencing a dengue fever outbreak, and the vector for dengue fever is the same as the vector for the Zika virus. And I would like you to tell the committee what recent developments there may be in terms of public health strategies relating to dengue and also to Zika.

Dr. COLLINS. So with dengue, the National Institute of Allergy and Infectious Disease just announced a couple of weeks ago success of a quad—I'm sorry—a tetravalent vaccine, which was tried out in volunteers and showed complete protection against dengue infection. And there is also a vaccine that has been produced by the company Sanofi that is already approved in a few places like Brazil and Mexico, but not yet in the United States. I know that Hawaii has had more than 300 cases of dengue, and there's a great interest in speeding up the process of getting access to that vaccine, and I would be glad to talk to you further about that, and Dr. Fauci, who directs that effort, would also.

In terms of Zika, the Zika vaccine efforts are on the fast track and we are doing everything we can to speed that up, but it will be until probably August or September before the first phase 1 trials can be initiated for human volunteers. And realistically, because then one has to go to phase 2 and 3 trials, this will not probably be generally available until 2018. We're also working on therapeutics as well as the vaccine.

CHILDHOOD VACCINATIONS

Senator SCHATZ. Dr. Collins, a new question. There is unfortunately a lot of confusion among young parents about the benefits and efficacy of vaccinating their children, and I would like for you to say as clearly and concisely and authoritatively as possible, what's your recommendation to young parents who may be reading things on the Internet and are otherwise well informed and certainly care very deeply about their children, but want to take the right advice?

Dr. COLLINS. Well, I really appreciate that question because there still is confusion out there, though I think the facts are now incredibly clear. There was a suggestion 20 years ago that there might be some connection with vaccination with the MMR vaccine and the onset of autistic symptoms. The report that put that forward ultimately was turned out to have been falsified. The author of that report has been stripped of his professional standing, and the paper has been retracted. But it started a concern, an understandable concern, amongst patients and parents about whether this might be a real connection. Multiple studies done over the course of these two decades in the United States and in other countries, especially Denmark, have repeatedly failed to show any con-

nection whatsoever between childhood vaccines and the onset of autism.

Autism is a terrible tragedy when it happens, we need to understand its causes, we are learning much about those, but what we can say I think categorically is that vaccines are not the cause. And, of course, it is very much an unfortunate circumstance if kids are not getting vaccinated and then fall ill from treatable diseases, like measles, which can even be fatal.

Senator SCHATZ. So your recommendation to parents is?

Dr. COLLINS. Get your kids vaccinated. Follow the recommendations from the professional societies like the American Academy of Pediatrics. Don't worry. This is a good thing. This will help your kids.

Senator SCHATZ. Thank you.

Senator BLUNT. Thank you, Senator Schatz.

Senator Cochran.

JACKSON HEALTH STUDY AND PMI

Senator COCHRAN. Mr. Chairman, thank you for this follow-up hearing. It gives us an opportunity to check in again with the status of what can be gleaned now from the Jackson Heart Study, which involved a cohort, a research cohort, of 5,000 men and women in Jackson, Mississippi, relating to the heart and the illnesses and consequences of heart disease. As you work to build a national research cohort, is this study going to be a part of that initiative in any way?

Dr. COLLINS. So the Jackson Heart Study, Senator, which you've been a wonderful leader for, and which you and I got to visit together 2 or 3 years ago, is a national resource to look particularly at the factors that play out in terms of cardiovascular disease in the African American community, where we know that the risk factors are particularly high. That study has already taught us a great deal about what those environmental and genetic and social and behavioral risk factors are turning out to be, and those 5,300 individuals who have volunteered to take part in this effort I think are real national heroes by their willingness to do so.

We are continuing to look for ways to connect up that effort with other kinds of studies, and I know Dr. Gibbons, who is the director of the National Heart, Lung, and Blood Institute, recently visited Mississippi to think a bit more about that with regard to other kinds of research going on in your State.

With regard to this Precision Medicine Initiative cohort, where we aim to enroll a million Americans, we very much open that door to every volunteer, and my hope would be that those who have already taken part in research studies would be particularly interested, and therefore, we might see particular interest coming forward from those folks who are already part of the Jackson Heart Study. Certainly, we learn more the more data that we have, and to be able to do that kind of connection would be quite useful. But we want everybody to have the opportunity to decide whether this is the kind of study they want to take part in.

Again, though, I can't tell you how much from NIH's perspective it has been valuable to have that already ongoing study now going on 20 years, or it will be in a couple more years, to teach us things

that you can only learn over the course of time, and which we also hope to learn from this cohort, the Precision Medicine cohort, as it gets launched in the next year or 2 and then moves forward going who knows how many decades to try to really understand all the factors that play out in terms of health and disease.

Senator COCHRAN. Okay. Thank you very much.

Senator BLUNT. Senator Shaheen.

Senator SHAHEEN. Thank you, Mr. Chairman.

Thank you, Dr. Collins, and all of you for being here this morning and for the work that you do every day.

ARTIFICIAL PANCREAS

So I have three questions, and I want to start with congratulating and thanking you all for continuing to make the artificial pancreas a priority. I was pleased to see that both in your written testimony, and although I didn't hear your comments, I know that you mentioned it in what you had to say. It will completely change the lives of people living with type 1 diabetes, like my granddaughter, Elle, who was diagnosed after her eighth birthday. So can you talk about what you hope to deliver in the next 5 years with respect to the artificial pancreas?

Dr. COLLINS. Thanks for the question. And of course, this is a very high priority for our National Institute of Diabetes, Digestive, and Kidney Diseases. The challenge is to come up with the kind of engineering, both tissue engineering and other types, that would reliably produce an accurate minute-by-minute measure of blood glucose and then deliver appropriately and safely the appropriate dose of insulin to keep those levels in the right zone. We all know that the current way that this is done, as your granddaughter no doubt knows every day, involves the sort of regular opportunity to find out blood levels oftentimes by a finger stick, and yet you can't do that every minute, and so there are peaks and valleys that undoubtedly are less than ideal. And we do know the better the control, the better likelihood of avoiding those consequences of cardiovascular and kidney disease and eye disease, which is very much our goal to try to prevent.

So the challenge here has been, because of the safety issues, to move this forward in a fashion where we know we are going to be doing good. There have now been a number of studies under very closely observed circumstances—

Senator SHAHEEN. Actually, my granddaughter participated in one of the initial studies for juveniles.

Dr. COLLINS. Wonderful. And those have shown very encouraging results. I think the reason of going cautiously is that, of course, an overdose of insulin can be extremely dangerous and even fatal, and so you want to be sure you have a failsafe system, and that's where a lot of the focus now is. But as I—

Senator SHAHEEN. And so—I'm sorry to interrupt, but my time is running. So do you think—are you optimistic that in the next 5 years we may have a device that is going to be available on the market for people?

Dr. COLLINS. In my opening statement, I said 10. I would love for it to be 5. I think it could be. It would certainly require both some good scientific effort and some good support for that, but also

some of the things we don't quite know yet. If they turn out well, yes, I think that is a feasible kind of goal, but I wouldn't want to overpromise.

Senator SHAHEEN. Because Europe is ahead of us on this, which is disappointing to see. Good for people in Europe, but we want to catch up with that.

HEROIN AND OPIOID OVERDOSES

Dr. Volkow, I want to follow up on Senator Capito's questions about the heroin and opioid epidemic because in New Hampshire, we are experiencing the highest percentage of overdose deaths of any State in the country. It is not just an epidemic, I believe, but a pandemic. We talked about this when you were here before us last year. And you know, I was at a forum recently where the local hospital CEO said that they can tell when there's a new batch of heroin on the streets within an hour because they see about a half a dozen people admitted into the emergency room. And so that's what we're dealing with.

So can you tell me what resources NIH, the Institute on Drug Abuse, has that can assist those people on the front lines? Because I think, as we talked last year when you were here, I think we have been very slow at the national level to respond in the way that this epidemic deserves.

Dr. VOLKOW. Yes. As an institute and the NIH does research, so the way that we have responded is to provide with products that allow us to address and prevent the overdoses from opioids, which, of course, is very tragic, and I am very, very aware of what's going on in New Hampshire.

Senator SHAHEEN. I know you are.

Dr. VOLKOW. One of them very successfully led to a product that was approved by the FDA last year, which is intranasal Narcan, that has many advantages, including the fact that it can deliver very high concentrations to the blood very rapidly, and that's fundamental to overcome an overdose. And this is particularly relevant now on selling because we are seeing that many of these overdoses are due to the fact that they are combining with Fentanyl—

Senator SHAHEEN. Yes.

Dr. VOLKOW [continuing]. Which is very, very potent. So note that regular Narcan may be as useful as we need stronger products. This product also is very cheap, it's something like \$37, so it becomes very, very available. That's one.

The second strategy that we've also shown decreases overdoses is medication-assisted therapy, but it's not being deployed.

Senator SHAHEEN. Right.

Dr. VOLKOW. And sometimes it's not just the issue of deployment, but the structure is not there for patients to be able to take advantage of it. Very problematic in rural communities. So we are developing again with pharma in a partnership medications that will be easier to comply with and that will require much less infrastructure to sustain.

But also we are doing research on implementation. How can we take advantage of the healthcare system so that they are involved in the deployment of medication-assisted therapy for individuals

with opioid use disorders? Because it has been shown to prevent overdoses.

Senator SHAHEEN. We're still hoping that you might be able to come to New Hampshire and talk about some of these new developments because I think it's the kind of thing that would be—is very important, and there was a lot of interest.

Dr. VOLKOW. I would welcome it, and I think they are arranging it.

Senator SHAHEEN. Yes.

Senator BLUNT. Thank you, Senator Shaheen.

Senator MORAN.

Senator MORAN. Mr. Chairman, thank you very much. Thanks to you and the ranking member for conducting this hearing.

Dr. Collins and others, thank you very much for your presence here.

SPENDING PRIORITIES

Dr. Collins, this wasn't my intended question, but I heard—I actually listened to the things you and others said in the panel this morning, and this is a response to what I heard. One of the things that you and I have talked about over a long period of time is how to prioritize spending within NIH, and you make decisions about what research receives a priority and what centers are receiving funding. You have appealed to me, and particularly in my time as the ranking member of this subcommittee, that we don't want the decisions to be made by Congress, we want science and medicine to determine, the researchers to determine, how money is spent at NIH, and you know, that's against our inclination. We have people who come to us who ask for help, who make suggestions of how we could improve their lives, their family members' lives. And I think all of us want to help, and you'd love to say we'll give NIH more money to cure or treat this disease. I have believed in the theory that those decisions are best made by science and medicine.

Do you have evidence—I mean, one of the things you said was we ramped up, “sped up” I think was your word, research in regard to Zika. What that would suggest to me, that if you can ramp up something to do that, do you not have to diminish something else? And so my question is, when you assure us that you're making priority decisions based upon science and medicine, when you increase spending someplace, is there a corresponding reduction in spending someplace else?

Dr. COLLINS. It sort of has to be that way, doesn't it? And this is one of the things that we very much tried to outline in this NIH Strategic Plan, which is now just 4 months out and which I think does lay out the difficult situation we face when we have something that really requires urgent attention, like Zika, there needs to be a way to pay for it. Now, obviously in that situation, the administration has proposed an emergency supplemental lacking so far a response because it's taking time, just yesterday, now the Department advising that we shift dollars away from other things to put into that. But already, if Tony Fauci was here, he would say he was doing that, and by necessity, to try to accelerate that.

So for all of us, as science managers, we are facing sort of Sophie's choices every day, especially in the course of the last dec-

ade or more where our success rates for grant applications have been the lowest in history, below 20 percent. And so one of the hardest things that each one of us at this table faces is that almost on a daily basis you have to turn away a science that you know is exciting, a science that is well designed, and science that is important for a particular public health need, but on the scheme of things, when you have to set priorities, which we're forced to do, it doesn't quite make that cut, and we know we're giving away opportunity.

Senator MORAN. Well, Zika perhaps is an example, but maybe not the best example, in the sense that——

[Cell phone rings.]

Senator MORAN. I didn't know anybody had my phone number.

[Laughter.]

Senator MORAN. I thought I was on the no call list.

[Laughter.]

Senator MORAN. Dr. Collins, the sense that we would make medical and scientific decisions, Zika comes as something new, something relatively new, and so we make choices of allocation there, but on an ongoing basis, you've indicated, you know, promising developments in many areas, but I assume when you say that, that means that if there is a promising development on the horizon, that means that you're making a decision to put additional resources, dollars, into that research at the expense of something less promising. Is that true?

Dr. COLLINS. That's absolutely true. That's our responsibility.

ALZHEIMER'S DISEASE AND DOWN SYNDROME

Senator MORAN. Okay. Let me ask a question about Alzheimer's, and particularly the relationship between Down syndrome and Alzheimer's. We've had this conversation, I don't know how recently, maybe even a couple years ago, but the beta-amyloid deposits and the scientific evidence that those appear in individuals by age 40 who develop Down syndrome, who have developed Down syndrome, and that often apparently a correlation between that and Alzheimer's. What's the latest knowledge that's been gained in regard to the relationship between Down syndrome and Alzheimer's?

Dr. COLLINS. Well, it's very clear that individuals with Down syndrome, who have an extra chromosome number 21, have a heightened risk of Alzheimer's disease as they get older, and they may very well develop that both pathologically and in terms of effect on the brain function by their twenties or thirties. This is presumably on the basis of the fact that the Alzheimer's amyloid protein deposits in the brain is on chromosome 21. So they have an extra copy of that and presumably, therefore, are making an excess amount of the protein, and ultimately it deposits.

This is a tragedy for kids who may have been functioning pretty well and then develop this problem in their twenties and thirties, but it's research-wise also an opportunity that we want to take advantage of, knowing that these are individuals at very high risk who themselves and their families are interested in interventions.

We are now mounting research studies with some of the new ideas about Alzheimer's prevention, specifically making those available to kids with Down syndrome who are in their twenties to see

whether in fact we can show benefit and in the process learn everything we can about both Down syndrome and Alzheimer's disease.

Senator MORAN. Thank you. Thank you, Mr. Chairman.

Senator BLUNT. Thank you.

CHEMOTHERAPY FOR BREAST CANCER PATIENTS

I'm sorry. Dr. Lowy, I was at the Siteman Cancer Center at Washington University a few months ago and just sitting around a table talking with doctors there on the topic of breast cancer. They said their view was that maybe most doctors who deal with breast cancer are coming to the conclusion that chemotherapy is usually not needed, but they don't know how to determine whether it's needed or not, that maybe as many times as 8 out of 10 times that the chemotherapy that a breast cancer patient goes through after surgery, it just wasn't necessary.

Comment on that generally and other things like that where both the patient and the cost could be dramatically impacted if we just had a little more information and more ways to identify a group of patients that we can clearly determine, "You don't need this, you're in the 2 out of 10 that do," "You do need it, you're in the 7 or 8 out of 10 that don't." Your thoughts on that would be helpful to me.

Dr. LOWY. Thank you, Senator Blunt.

First I want to thank you, Senator Murray, and your colleagues for the incredible strong support that you have had for NCI and all of NIH.

Your question is critically important, and we are optimistic that the future of predictive oncology has enormous potential, the question of: How do you deliver the right drug to the right patient at the right time? And an important aspect of that is: Who should be treated and who should not be treated?

We need to do two different kinds of research in order to establish that on an evidence-based manner. The first is to do more pre-clinical studies so that we understand the biological basis for the different prognosis for different patients with breast cancer. And the second is to do clinical research particularly through understanding large datasets that have been discussed earlier in the hearing to understand the patient responses and whether patients actually need this through large databases with genomic analyses, et cetera, that Dr. Collins referred to earlier. Through this combination, we will get to the point of being able to tell who is better to give more treatment to and who less.

Senator BLUNT. I think for those of us who are the ultimate laypeople in part of this discussion, having a few things like that that we can mention as possibilities make a difference. It certainly begins to make the case for how this research impacts individuals, how the research impacts overall healthcare costs, how the research leads to more opportunity for people and families, and it's just helpful for us to have.

ALLOCATING ALZHEIMER'S DISEASE FUNDING

Dr. Hodes, if you know, looking at what you're looking at with Alzheimer's, as an example, how much of a factor is determined on how you allocate research dollars based on what you see as a grow-

ing problem rather than a more stable problem? Alzheimer's would be an example of your numbers.

The committee asked you a couple of years ago to do some forward projections on this. You did. If your projections are anywhere close to correct, it's an astronomical problem, and I assume that has impact on how quickly you apply research focus there, but your thoughts on that would be helpful.

Dr. HODES. Thank you for the question. You summarized yourself very well the projections for cost, and of course, the cost isn't just dollars, but above all, is human suffering until we are successful. The increased funding that's been provided is being applied to research, research that's directed according to a plan very much based on best expert opinion, which sets up priorities, milestones. What we need to do each year to achieve with greatest optimism, at least the goal of the national plan, that is an effective intervention by 2025, it's an aspirational goal, it's a hope for goal, and so you're quite right, as we allocate resources in this area, we allocate across the spectrum, the most basic research to discover new targets, because we don't know that what we know now is ultimately what's going to give the best cure. Also, the translation of our current best targets into clinical trials. And the great hope we have now, I think, in the field, that by intervening in a way we couldn't just a few years ago in the disease process long before there are symptoms, we have an opportunity to arrest damage before it perhaps occurs irreversibly with death of brain cells and so on, all of this, as you say, driven by the suffering of people today as well as by the demographic projections of how great this problem will be and even increased magnitude in years to come because of the success we've had in increasing life expectancy and health span in so many other respects.

Senator BLUNT. Thank you.

Senator Murray.

BIG DATA FUNDING

Senator MURRAY. Thank you. I want to go back and ask Dr. Koroshetz a question on the big data. How much of the funding in your request is going to be dedicated to creating data centers in the fiscal year 2017 budget?

Dr. KOROSHETZ. Yes, thanks. We have been thinking about this for a while. You know, the BRAIN Initiative starts out primarily developing new technologies, so that's currently in the space we're in now. So not a lot of big data coming in yet, but the expectation was that at about 3 years, which is going to be fiscal year 2017, that we would start moving into actual experiments that look at brain function in humans as well as animals, and so we are going to be challenged now with building the data platforms that will allow this work to happen on a collaborative basis.

Having been at the Allen Brain Institute, you may have seen, they have a tremendous, tremendous data platform for the work that they're doing. And so, we have multiple different groups, doing different areas of research, and those groups are actually working out, what is the best data platform for them at this point. We expect in 2017, we will spend \$5 million a year on data platforms.

Senator MURRAY. \$3 to \$5 million. Okay.

And Dr. Collins, let me go back to you. The challenge isn't unique just to the BRAIN Initiative, it's across NIH. What are you doing to make sure that we have common standards established across the entire enterprise to avoid creating incompatible systems and practices?

DATA SYSTEM STANDARDIZATION

Dr. COLLINS. That is a very important challenge and responsibility. And again, as part of this Big Data To Knowledge, BD2K, program, we are actually funding something called a Data Discovery Index, which is one of our centers for data science, and basically this is attempting to come up with standards where data that's been produced on a wide variety of research studies, from basic to clinical, can be accessed by individuals who are looking for it without having to run through all kinds of incompatibilities. This is a challenge, but I think one that we're making some significant progress on. Obviously, it's easier if we do these things prospectively than trying to retrofit databases after the fact, and so there's a lot of focus in that space.

What we're dreaming of, and which we have actually some significant pilot projects underway on, is a data commons where basically all of this information finds its way into a common space with standards, with appropriate so-called metadata, so when you get a data file, you know what it is and how it was derived and——

Senator MURRAY. Housed at NIH?

Dr. COLLINS. Probably in the cloud, but potentially our investigators contributing to it, and we would need to, as part of grant funding, supply the resources to make that possible.

DIVERSITY IN MILLION-PERSON COHORT

Senator MURRAY. Okay. And let me just quickly ask you about the million-person cohort again. I am concerned about diversity, and I just wanted to ask you again, how do you make sure you're doing it and working with experts that you avoid the risk of bias that could affect the cohort's usefulness if it isn't a diverse trial?

Dr. COLLINS. We want very much for this to be a generalizable cohort, which means we need to have overrepresentation of groups that are traditionally underrepresented. So that means minorities, that means individuals from lower socioeconomic status. We will look carefully when we open this up to direct volunteers and begin to try to see how we're doing as far as bringing such individuals in, and we'd be concerned that they might not be coming in as large numbers as those who are more in the majority population.

A big effort is going to be for us, through the community health centers, to try to see how we could use, in an unprecedented way, those centers which give care to more than 10 million people, also as an opportunity to carry out research, recognizing that we want people involved in this study not to think of themselves as subjects, but as partners, as full participants, in this effort, and we will approach them in that way.

Senator MURRAY. When do you expect to have the details of that worked out and are going to be willing to share them?

Dr. COLLINS. So we already put together the overall plan. It was published last September as far as the design, the Precision Medi-

cine cohort. We're now trying to figure out how to implement that. Later this year, by the fall, we'll have a much better sense of exactly how successful we're going to be with those various inputs.

Senator MURRAY. Okay. Thank you. Thank you very much.

Senator BLUNT. Thank you, Senator Murray.

Chairman Cochran.

RECENT BREAKTHROUGHS

Senator COCHRAN. You may have just answered the question I was going to ask, but I'm going to ask it anyway. Do you have any recent breakthroughs that you can announce or tell the committee about as a result of investments that we have funded through the appropriations process here in Congress?

Dr. COLLINS. One of the things that's a great privilege for me is to write every Tuesday and every Thursday a blog, I hope some of you are reading my blog, but I bet you're not, but I would encourage you, if you have a couple minutes, to do so. And as part of that, I survey across the whole landscape of biomedical research to see what new things have just appeared in the published literature that are particularly exciting. And so every time I have the chance to do that, there's a new story.

Today's story, if you read the blog, which came up, I guess, about an hour ago, is about a engineer who has developed the kind of sensor that you could use for measuring all kinds of body performance properties, including glucose, if you wanted to use this as part of a artificial pancreas, but the sensor is designed so that it's not this rigid metal structure, which probably wouldn't work very well in the body, it's flexible, and this is an interesting sort of materials issue. If we are going to come up with ways to monitor all kinds of ways in which our bodies are performing in health or disease, we need these kinds of sensors to be very durable and to be possible to not interfere with function, which means sort of rigid structures may be not such a great idea. So that's today's blog, for instance.

But looking across the board, goodness, some of the things that are happening in cancer right now, I guess I'd have to point to particularly something I mentioned in the opening statement that relates to President Carter, the ability to activate the immune system to tackle cancer cells that you know the immune system ought to be able to see, but somehow it's been masked, and we can unmask it with things like checkpoint inhibitors or actually taking immune cells to school and teaching them how to go chasing after the cancer that they haven't noticed, and to figure out how you might take those advances, which have changed everything for people with melanoma and leukemia and lymphoma, and figure out, how does it work for pancreatic cancer and how does it work for brain cancers, where we are not as successful? That's a big push. That's one of the reasons for the Cancer Moonshot that the Vice President is now promoting.

And I guess I should ask Doug Lowy to say another word or two about why we see this as such an exciting moment and why there are some breakthroughs already happening, but more to come.

Dr. LOWY. Senator Cochran, let me give a two-part answer first to your question and then what Dr. Collins has mentioned.

The excitement in immunotherapy is matched by the fact that immunotherapy started really with basic research quite a long time ago with support from NIH specifically at NCI, and what we are seeing is almost on a monthly basis the surprising finding that checkpoint inhibitors progressively have beneficial effects in more and more cancers.

The Vice President's Moonshot Initiative, an important part of it is to try to understand and utilize combination treatment so that we use combinations of immunotherapy, combinations of targeted treatment, and intersection between those so that we can get better responses and target a much broader percentage of people who have cancer.

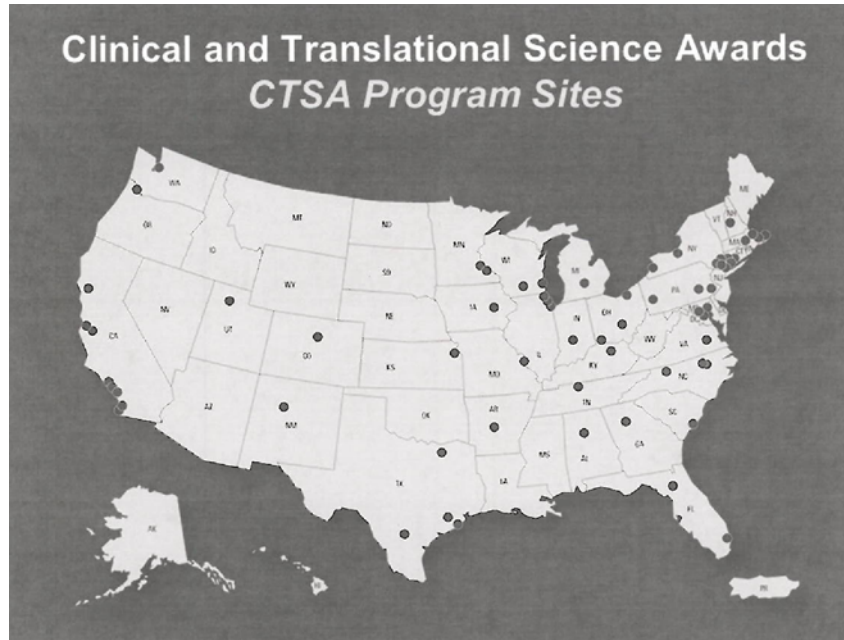
But the Moonshot goes far beyond that, and it looks at cutting edge research opportunities that have been created as a result of new understanding, and new understanding of the dynamics of this, and putting them together so that we can make accelerated progress in prevention, screening, treatment, and basic research.

CLINICAL TRANSLATIONAL SCIENCE AWARDS

Dr. COLLINS. If I may, one of the things I think that the public is particularly excited about is when we have a clinical breakthrough, and Dr. Austin has not had a chance to speak, but I wanted to ask him to say a word about where we are by building this national clinical research network called the CTSA's, which is in a phase of coming forward with a number of ways of accelerating that part of the research enterprise. It's pretty exciting.

Dr. AUSTIN. Yes. So thank you. As you all know, the current numbers are, it takes about 15 years to go from a discovery to a new intervention, a new drug, for instance, and another 15 years before it reaches all the patients that need it. That's always been a problem, but it's a particularly heartbreaking problem now given how many opportunities there are. So our Center is focused on the general issues that prevent that from happening faster, and our aim is to decrease that time by tenfold and increase the efficiency by which it happens. That's our goal, and I think it's achievable.

[The graphic follows:]



Dr. AUSTIN. The biggest part of that, the year, those years, happens in the time when we're testing in people. There are many things that can be done through the CTSA program, which is this unprecedented program that NIH has of academic medical centers all over the country which have been previously—oh, so there they are, that's where they are, in many or most of your States, and they have connections to the—all the ones that don't have little dots there, connections to all the States in the Union. And what we've been doing is to tie these together into a collaborative national network for translational medicine such that patient clinical studies, multisite clinical studies, can get started up, recruited, completed, much more quickly and with much higher quality, and we've done this through a national network for IR, or Institutional Review Board standards of subcontracting, a national way to do recruitment for any clinical trial, it doesn't matter what the disease is, and novel clinical trial designs. So those are just some of the things that we're doing through the program. And I really do want to thank you for your support in doing that because it's really been critical to us.

Senator COCHRAN. Thank you very much.

Senator BLUNT. Thank you, Chairman.

Senator Shaheen.

NIH/DHS PARTNERSHIP

Senator SHAHEEN. Thank you, Mr. Chairman. I very much appreciated getting a copy of this NIH-wide Strategic Plan. I haven't had a chance to review it completely, but I wanted to ask a question that puzzles me as I look at the list of your frequent Federal partners and see many agencies that I would expect and departments

I would expect to be on the list: DOD, EPA, Veterans Affairs. But what is not on this list is the Department of Homeland Security, and I found that puzzling because we had a hearing yesterday before our subcommittee of Appropriations where we heard from the DHS Office of Health Affairs, their Domestic Nuclear Detection Office, the Science and Technology Office, and they talked about some of the things that they're working with respect to workforce issues for both mental and physical health. And so I'm just puzzled by whether that's an omission on this list or whether you don't work with them regularly, and why that is.

Dr. COLLINS. That's a great question. We do work with them in terms of particular topics of shared interests, such as, for instance, concerns about bioterrorism. I think the list that you see in the strategic plan is more about agencies where we share research projects, where we're putting dollars together into something to try to do a research study and get an answer. Our work with Homeland Security is really much more about policies, and we see them quite regularly when it comes to that, particularly when it comes to concerns about infectious diseases.

Senator SHAHEEN. That's helpful. The hearing yesterday actually was on their R&D efforts, and so there was some overlap, and I just—I'm always concerned about the silos that I think too often we work in, in government and the need to coordinate and cooperate across agency portfolios so that we get the benefit of what everyone is doing.

Dr. COLLINS. I appreciate your pointing this out, and it's something I will personally look into to see whether it could be in fact we are working with them in an R&D project and I just didn't know about it and didn't put it in that plan. But I will follow up on that.

Senator SHAHEEN. Thank you. I appreciate that.

Thank you, Mr. Chairman.

Senator BLUNT. Senator Cassidy.

UNIQUE IDENTIFIERS IN BD2K

Senator CASSIDY. Hey, Dr. Collins, a couple other things. As I look at your BT—your Big Data To Knowledge initiative, and you speak about having centralized data where people allow their EHR (Electronic Health Record) information to be transferred, obviously, some folks will be in multiple EHRs. That suggests to me that you've some way decided on a unique identifier, means of identifying. On this panel and this Senate, there is some concern about unique identifiers, however they be. So do you want to give an in-depth—if you think it's too in depth, but if you could point me in the direction because we are trying to understand the use of unique identifiers, et cetera.

Dr. COLLINS. Very important and complex topic. Purely from a research perspective, it would be wonderful to have unique identifiers so that we could deal with circumstances where we have data on the same person coming from multiple directions. We understand the concerns that many have about the use of such identifiers, and so we are not counting on that becoming a reality, and instead, it becomes necessary to use other kinds of algorithms to try to disaggregate records that appear to be from the same person,

but might not be. And of course, oftentimes one tries to do that with simple things like birth dates and middle names and so on, but there will be times where we don't get that right.

The good news, I guess, is that we're talking about very large studies where in fact if we are unable to utilize a few records because we can't be sure of their particular provenance, we may just have to set those aside.

Senator CASSIDY. The answer you just gave suggests that it won't be a passive process where somebody will designate my records shall go, but there will be some sort of outreach from the database searching like a bot, where did Bill Cassidy show up as you search, and then to pull in there's a Bill Cassidy that previously consented for his data to be—is that correct?

Dr. COLLINS. That is correct, because we understand the sensitivities about not having electronic health records with personal identifiers being stored in one common dataset where there might be more of a potential for hacking problems.

STORAGE OF BIOSPECIMENS

Senator CASSIDY. Now, in that case, I've looked at it, much of what your PMI (Precision Medicine Initiative) has done is said to be centralized, but it sounds as if your EHR aspect will be federated in that my record will reside in Louisiana, but nonetheless, here in D.C., my blood sample would be kept, my hair, my nail clipping, and somehow that has reached out to where my primary care physician is in Baton Rouge. Is that fair?

Dr. COLLINS. With regard to the biospecimens, we anticipate that in many instances these are people who part of health provider organizations and there obtain the biospecimens, but we do intend to have a biobank which is centralized where all these specimens are stored and kept over many years of time. So, yeah, you're right, that will be centralized even though the details of the electronic health record will remain with the patient.

Senator CASSIDY. Now, I've read an article by Keith Yamamoto and heard a lecture by him. I know he's been on advisory boards.

Dr. COLLINS. Yes.

Senator CASSIDY. Very impressive, talks about the Google Map aspect of it. Again, your thinking prepared me for this, but the genomes, the microbiome, the exposures, behaviors, clinical tests, and EHR. Now, the expense of that is going to be enormous. So is your initial PMI going to include all these layers, or would that be something that we move towards?

Dr. COLLINS. The latter. It's a very important question. We're going to start off very simple to both try to save costs and try to be sure we have this set up in a fashion that is completely robust. We don't, in fact, even anticipate doing much DNA analysis on individuals who join just from blood DNA for the first year or so, and certainly the idea of adding a microbiome part, which many of us are excited about, would be downstream. That will help us because the costs of those analyses are coming down, as you know, quite dramatically. Right now, we could not afford, with a million people, to do all the things that we'd like to, but if we stretch that out over the coming years, the costs will come down, and we think we can afford to add those things as we go along.

Senator CASSIDY. Going back to the business model, though, I can see where, okay, so gut flora can influence obesity, for example.

Dr. COLLINS. Yes.

Senator CASSIDY. So we'll be swabbing gut flora. But I guess I keep on going back to the business model because I can see this terabytes and terabytes growing, so it not only grows in terms of terabytes, but in terms of its bite on the NIH budget, the cost to accumulate, to maintain, longitudinally on a million people, and from your aspect, you actually want to grow that million to a larger number.

So I see that California has begun their own Precision Medicine Initiative. I can imagine other States might as well, both as an economic driver as well as an aid. I don't know how far your business model is going down, but I can still see a federated model of this where instead of everything centralized, just as you federated the EHR, so you've federated some of this other.

There's a unique population in Louisiana of young pre-menopausal black women who have triple negative breast cancer, and another group of folks of Cajun extraction at high risk for colon cancer. I have tremendous interest in my State because I want to address both the needs of these women and these men. It seems more practical that that would be domiciled, all that specimen, et cetera, in Louisiana than there; the women are in an impoverished area of the State, as an example.

So anyway, any thoughts about that, a federated model of the whole setup as opposed to—

Dr. COLLINS. I think part of the conversation is distinguishing between the Precision Medicine Initiative, which is this explicit now designed cohort of a million people, and Precision Medicine writ large. I think the concern I would have is that we not try to have the initiative take on all of the opportunities that now exist in Precision Medicine. They should be also going forward supported by all of the NIH Institutes and other sources as well. And it will serve us well, I think, best at the present time if the million-strong cohort keeps a very simple approach and doesn't focus on any specific diseases, but tries to enroll a generalizable population on which other studies can then be layered.

Senator CASSIDY. A follow-up question, but you may tell me I should do a QFR unless you're going to give me an allowance for one more.

[Laughter.]

Senator CASSIDY. Forgiveness, not the permission.

[Laughter.]

DUPLICATIVE DATASETS

Senator CASSIDY. But that tells me then that we're actually going to have duplicative efforts because I think I've read that there are 70 different datasets at NIH, and so logically—now, I may not have that quite right, but each institute has its own dataset, and there is some effort to coordinate, but that means that we're going to have these 70 different datasets and we're going to have the PMI, the Precision Medicine Initiative, Ken Mandl has written so well, that really we don't need to have all these different datasets plus, rather, we need this to be able to bring in these different datasets.

We're trying to find you funding, but, again, I see this initiative taking more and more of what Senator Cochran is going to give you. And if we could integrate, now that you've thought about this, if we could integrate this, why not, if you will?

Dr. COLLINS. Well, maybe I didn't explain this as clearly as I should have. The Precision Medicine Initiative has had its budget sort of thought through, and that's in the proposal that came out in September, and right now for fiscal year 2017, proposed at \$300 million. They need to ramp up to about \$500, but not to go beyond that. But let me be clear, the institutes at NIH all look at this million-strong cohort and think, wow, what a great platform on which we could layer all kinds of other studies. With a million people, there are going to be tens of thousands who have a particular condition already consented for research, already with background information.

So a lot of the studies that we have been doing in the past, by setting them up de novo, which is expensive, and then running the study and then closing it down, can now be done much more efficiently by utilizing this platform for whatever it is that we need more information about. I think ultimately this saves us a lot of money over what we currently spend in clinical research.

Senator CASSIDY. Okay. Thank you. I yield back.

Senator BLUNT. Thank you. Well, Senator Cassidy figured out how to get his second and third round at the same time.

[Laughter.]

Senator BLUNT. You know, on the national children's study that was done a few years ago, this diversity topic at the end of that study I think became one of the more questioned parts of the study, so a lot of these questions I think are helpful. There will be—the record is going to stay open for a week for additional questions, but is there anything while we're all here for another 5 minutes or so that you or any of your colleagues would like to address?

The written questions are good, and they're particularly good for people who have submitted them. I'm not sure that very many people look at the questions they didn't ask in the written questions. So is there anything here—we almost left Dr. Austin out. Is there anything here that any—Francis, Dr. Collins, that any of you want to bring up?

Dr. COLLINS. Any of you want to volunteer a point that you didn't get to make that you thought would have been particularly timely?

Dr. LOWY. Thank you, Senator Blunt. I think that you all have a copy of the New England Journal of Medicine perspective that Dr. Collins and I wrote and was published earlier this week about the Vice President's Moonshot Initiative. Dr. Collins and I and my colleagues at NCI, as well as many extramural people, are working closely together to try to develop what we think are going to be incredible opportunities for cancer research to benefit patients. This effort really goes from basic science all the way to implementation, and thanks to your strong long-term support, we are poised to accelerate progress thanks to this proposal.

And we have a blue ribbon panel that is going to be reviewing what we currently propose as well as looking forward to receiving other potential enormous opportunities. We are not trying to cover

the entire waterfront of cancer research, but instead, to point to specific opportunities for research that will be bold, feasible, and have an impact in basic prevention, screening, and treatment.

Thank you.

Dr. KOROSHETZ. Yeah, I would just like to talk a little bit about the question of priorities that came up and just make the point that if you look at the history of advances, you can't predict where they were going to come from. And so I think it's tricky to say, you will get a certain result if you put money into that I think Zika is a great example. It turns out that one of the investigators who was working on the BRAIN Initiative to develop ways of identifying all the different cell types in the brain is the one who found out how the Zika virus was getting into the brain. He had nothing to do with Zika, but that technology turned out to be beneficial, and there was no way of predicting this.

Our major advance lately was a study using a diabetes drug. The study was 17 people who had a stroke, and also but didn't have diabetes had an abnormal glucose metabolism. We treated them for 5 years with a diabetes drug, and their stroke risk dropped by 24 percent. So, again, this is something that you couldn't have predicted, but retrospectively, it kind of makes sense.

And so I just urge the committee to think about this importance of the foundational basis of research, which is critical. Targeted research is risky in the sense that you're putting your money on one horse. You don't actually know all the time which horse is going to win.

Senator BLUNT. Anything else?

Dr. COLLINS. I'll just add to what Walter said about the convergence both of science that comes from unexpected directions, but also about scientific disciplines that have increasingly come together. You mentioned your experience of seeing how engineers are playing a role in biomedical research in really exciting ways. That's happening all around us, and the idea that we have to have physics over here and chemistry over there and biology over there, engineering over there; not anymore. These are all very much now coming together in an integrated way.

I guess I would just like to say, because I've now been at NIH for some 23 years, it was real poignant today walking from Union Station over here to this hearing, passing by the pink dogwoods and tulips that are blooming along the sidewalk and realizing this is probably my last opportunity to appear before all of you distinguished Senators.

People have asked me since I became NIH director 7 years ago, "So what's that part like where you have to interact with the Congress?" and I always break into a smile and I say, "It's one of the favorite things that I get to do because I get to sit in the room or in a hearing with very substantive people who are trying to lead our country in the right direction and talk about medical research, and it's a topic that everybody is interested in, and it's not partisan, and it's not political, and everybody wants to do the right thing." And I can't think of a single one of those interactions that went badly, and I'm happy to say today has added to that list of things that actually went really well.

And so I just want to thank you, the four of you still here, and all the others who aren't here, but who I've had the chance to talk to, hundreds of them, over the course of this time, for your dedication to our country, for trying to do the right thing for all the people out there whose hopes and dreams are rested upon progress in this area, because everybody cares about health and everybody hopes that there will be something there for them if they fall ill.

You are doing wonderful work. We are thankful to you for what you've done and hopeful for what you may be able to do this year, even in what is undoubtedly a challenging time. So thank you.

Senator BLUNT. Well, thank you, Dr. Collins, and you've done a great job leading the organization. Every time you suggest this could be the last time you're doing something, I'm always here to encourage you not to rush out the door.

[Laughter.]

Senator BLUNT. There are plenty of things yet to be done, and I would be personally pleased if you continue to be a big part of those things to be done.

Also, I think comments were just made, it's so important to us to realize that you can't prescribe results, and not to become overly prescriptive in the work that you do or how you do it. The Thompson Center I mentioned earlier at the University of Missouri deals with autism. Somebody from the engineering department is very engaged in trying to find an early way to detect autism in very young children with some equipment looking at eye examinations, no medical background, but a very important part of that team, and you know, what Walter mentioned, is discovering things you don't think you're going to discover, and we don't want to build walls that make it impossible for you all to have that kind of flexibility and determination.

ADDITIONAL COMMITTEE QUESTIONS

So thank you for today. The record will stay open for one week for additional questions.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

"SURGE" FUNDING

Question. NIH received 2 year "surge" funding in fiscal year 2009 and fiscal year 2010 as part of emergency funding contained in the American Recovery and Reinvestment Act of 2009. Dr. Collins, can you discuss what happened in fiscal year 2011 when this "surge" funding was not maintained and NIH had approximately \$5 billion less in funding than it did the year before?

In particular, as we think about the appropriate upward funding projection for NIH, would you ever want funding to decrease at a given point?

And what happens to the research infrastructure the first year funding is reduced?

Answer. Everyone was aware that the \$10.4 billion NIH received under the American Recovery and Reinvestment Act (ARRA) would be one-time funding. It was spent in a way that did not create out-year commitments, either by providing full funding for a multi-year research project up front, or by making capital investments such as construction projects. As a result, the return to a more typical funding level in fiscal year 2011 did not have the same impact as a reduction in annual funding.

NIH usually awards grants for multiple years, with each year's funding coming from the current year appropriation. Whenever possible, an increase in appropria-

tions is used to make more new and competing grants. Those grants will continue to require a similar level of funding in the out years, as noncompeting grants. With flat or decreasing funding the next year, the number of new and competing grants is likely to decline, as the prior year increase has to be used for the additional noncompeting grants. The optimal scenario is increasing funding at a steady rate; that allows the number of new and competing grants to increase each year.

If it is clear in advance that a funding increase is one-time rather than recurring, NIH can take steps as it did with ARRA to avoid a negative impact the following year. A reduction to recurring funding, especially a large reduction, would be damaging to NIH. For example, in fiscal year 2013 there was a major reduction in funding due to sequestration. Compared to fiscal year 2012, the number of new and competing research project grants (RPGs) declined by more than eight percent, and noncompeting RPGs had their funding cut by nearly 5 percent on average. The number of National Research Service Award trainees declined by almost five percent, and approximately 7 percent fewer new patients were admitted to the NIH Clinical Center.

DRUG REPURPOSING & CLINICAL AND TRANSITIONAL SCIENCE AWARDS

Question. Dr. Austin, clinical trials are key to developing treatments for disease, but I often hear that they are quite time consuming and costly. What is NCATS and its Clinical and Translational Science Award program doing to improve the clinical trial process?

Answer. NCATS is grateful to the committee for its fiscal year 2016 support of the Clinical and Translational Science Awards (CTSA) Program. We define translation as the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public—from diagnostics and therapeutics to medical procedures and behavioral changes. Through the CTSA Program and its extensive network of research institutions nationwide, NCATS is developing innovative solutions to improve efficiencies and the quality of clinical and translational research. Our Center also supports multiple efforts to repurpose existing drugs and compounds for potential treatments for other diseases and conditions; however, because these repurposing programs do not directly relate to the clinical trials process, our response is limited to the NCATS CTSA Program.

NIH's Institutes, Centers, and Offices have a long, distinguished history of funding landmark clinical trials including those for coronary bypass surgery, treatments for breast cancer, and anti-retroviral drugs for people at high risk for HIV/AIDS infection. NCATS is addressing issues common to all clinical trials with a focus on approaches to harmonize and streamline multisite clinical trials, which are more complicated to initiate because each trial site currently follows its own business and research practices. This continued work to improve clinical trials research builds upon our Nation's success as a leader in biomedical discovery and provides a competitive advantage in developing, demonstrating, and disseminating innovations that help get more treatments to more patients more quickly.

One NCATS approach is the development of a more efficient review and approval process of multisite clinical trial safety using a single Institutional Review Board (IRB) model. Currently, clinical trial researchers cannot begin recruiting participants until an IRB performs an ethical review of studies involving human subjects. IRB review often slows down a multisite clinical trial because the different sites must address inconsistencies across the different IRBs. The single IRB model streamlines IRB review by having sites rely on a single IRB without compromising ethical principles and protections. Through the CTSA Program, NCATS has supported demonstration projects of single IRB models and is moving toward a model that will be used throughout the CTSA Program network. And, in 2016, NCATS will announce CTSA Program Trial Innovation Center awards to fund centers that will network with existing CTSA Program hubs to facilitate multisite clinical trial implementation, including use of a single IRB model.

Another CTSA Program goal is to support recruitment efforts for clinical trials. Multisite clinical trials may require substantial subject sample sizes to credibly test hypotheses, and trials often are delayed or even fail entirely due to challenges in recruiting participants. To help combat the challenges, NCATS will issue awards in 2016 for CTSA Program Recruitment Innovation Centers. These will strengthen the CTSA Program's network capacity by addressing longstanding issues associated with multisite clinical trial recruitment, including access to data on the availability of potential participants; recruitment strategies that employ innovative approaches from other fields such as communications; and engagement of relevant stakeholders

(e.g., potential participants and referring clinicians) early in the recruitment process.

PRECISION MEDICINE INITIATIVE

Question. As you continue to shape the Precision Medicine Initiative (PMI), have you considered what projects other countries are working on to further personalized medicine and whether they are complementary or competitive? For example, both Great Britain and China have PMI programs.

Answer. As you are aware, during its planning efforts, the PMI Working Group of the Advisory Committee to the Director (ACD) engaged many individuals and organizations across industry, nonprofits, and academia to ensure that Federal funds dedicated to the PMI Cohort Program are used to fill gaps and not duplicate effort. The PMI Working Group, for example, was constituted of nationally and internationally renowned experts in a variety of precision medicine relevant areas and represented industry, nonprofits, academia, and the participant communities, including Sir Rory Collins, who leads the UK Biobank. NIH continues to interact with industry, nonprofits, and academia with other efforts and cohorts, including Google's Baseline Study, patient groups, NIH's own funded cohorts, and Department of Veterans Affairs efforts like the Million Veteran Program, as well as the growing number of international research precision medicine-oriented cohorts. NIH's ongoing interaction with these important organizations will allow opportunities for appropriate, mutually beneficial coordination to emerge as the PMI Cohort Program develops.

Question. At the White House PMI Summit event in February 2016, all of the patients presenting precision medicine success stories attributed those successes to genome sequencing, specifically. Yet, to date, no plans have been announced for collecting sequencing data from PMI participants. Why is that? Are there plans to do so?

Answer. NIH has consistently identified the collection of biospecimens for laboratory and genomic analyses as a critical component of the research cohort. The award to establish a biobank to receive such specimens will be issued this summer. Once the biobank is established, then the PMI Cohort Program may begin specimen collections, processing, and storage to be conducted over the next 4 years, during which time the timing and platform for genomic analyses will be identified and implemented.

Question. How will NIH ensure the full participation of women and minorities in PMI?

Answer. The PMI Cohort Program intends to enroll one million or more U.S. volunteers representing all life stages, all health statuses, and all regions of the country, with a special emphasis on enrolling those who are historically underserved by biomedicine and underrepresented in biomedical research. We project that the majority of the one million volunteers that will be enrolled by the end of 2019 (around 70 percent) will join directly through the healthcare provider organizations (HPOs, including federally Qualified Health Centers), and the balance (around 30 percent) will enroll directly into the Cohort ("direct volunteers"). The enrollments of the Cohort through both streams will be carefully monitored to ensure that our outreach and enrollment approaches are reaching a broad range of U.S. participants, including women and underserved communities that are historically underrepresented in research.

Question. Is NIH working with the National Center for Health Statistics or other Federal partners that fund or conduct large, representative surveys to understand the biases in the PMI million person cohort?

Answer. The PMI Cohort will not attempt to be a representative sample of the United States. Rather, the PMI Cohort will build a very large and very diverse cohort of participants from across the United States. This will allow the PMI Cohort to establish generalizability using a different approach: by having a diverse sample, it will have many subsamples that are composed of members of specific subgroups. By having a large sample, those subsamples will be large enough to develop estimates of effect and association for many of those subgroups. That will allow researchers to judge how similar those estimates of effect and association are across a variety of subgroups within the PMI Cohort, and thus to establish the generalizability of their findings. The development of this approach included extensive consultation and input from expert advisors through the ACD PMI Working Group process.

ENROLLMENT DATA

Question. The GAO recommended that the NIH Director should make Institute-level enrollment data available through public means, such as through NIH's regular biennial report to Congress on the inclusion of women in research, or through NIH's website. How is NIH moving forward with this recommendation?

Answer. NIH posted the most recent Institute/Center (IC) biennial inclusion reports for the fiscal year 2013–2014 biennial reporting cycle in early May 2016 at a newly created website: https://report.nih.gov/recovery/inclusion_research.aspx.

NIH ICs currently provide their IC-level enrollment information during open, public sessions of their Advisory Council meetings along with a written report certifying their compliance with the NIH inclusion policy, and they will continue to take this action at least biennially in accordance with NIH procedures for biennial reporting of inclusion. As noted in NIH's initial response to the GAO report, NIH had already begun efforts to standardize the reporting format for the ICs as part of the ongoing NIH Inclusion Re-Engineering Project that began in 2011.¹ NIH is continuing efforts to standardize a minimum set of data tables and graphics for each IC to use for biennial inclusion reporting, in addition to any additional analyses the IC would like to provide. The standardized reporting format will be completed before the fiscal years 2015–2016 Biennial Inclusion Report is due to be produced and posted in 2017.

TUBERCULOSIS

Question. The number of tuberculosis cases in the United States rose last year for the first time in 23 years according to the Centers for Disease Control and Prevention. What progress has the NIH made on developing more effective treatments and vaccines?

Answer. Tuberculosis (TB) research, including the development of effective therapeutics, vaccines, and diagnostics, is a top priority for the National Institute of Allergy and Infectious Diseases (NIAID). NIAID supports a broad range of basic, translational, and clinical research on TB in the United States and abroad to combat TB, including the growing threat of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. As TB is the leading cause of death in HIV-infected individuals worldwide, NIAID also supports TB research through its HIV/AIDS clinical trials networks to test TB therapeutics in the setting of HIV co-infection.

NIAID is currently implementing the President's National Action Plan for Combating MDR-TB. TB research objectives outlined in Goal 3 of the Action Plan, Accelerate Basic and Applied Research and Development to Combat MDR-TB, are being addressed by NIAID in collaboration with partners at CDC and USAID. NIAID is leveraging current and past investments in biomedical research to inform critical scientific areas of TB research and to facilitate development of new drugs, vaccines, and diagnostics to help prevent TB and the emergence of MDR-TB.

As part of its TB research portfolio, NIAID offers preclinical services to TB researchers in academia and industry to help bridge gaps in the product development pipeline and advance promising countermeasures to combat TB. NIAID resources have contributed to two-thirds of clinical TB therapeutic candidates and approaches currently in development. NIAID support has helped advance several candidate TB drugs, including SQ109 developed by Sequella, Inc., and Pretomanid developed by the Global Alliance for TB Drug Development. NIAID scientists were instrumental in the development of both of these drugs. Additionally, an NIAID-supported clinical trial will soon test two new drugs for MDR-TB, bedaquiline and delamanid, singly and in combination in patients with and without HIV co-infection. NIAID scientists also participate in the "TB Drug Accelerator" program, an innovative public-private partnership coordinated by the Bill & Melinda Gates Foundation that brings drug companies together to share their chemical libraries with researchers to assist in the identification of novel TB drug candidates.

NIAID also has made efforts to improve existing therapeutics for drug-susceptible and drug-resistant TB. Clinical trials are underway to evaluate novel treatment strategies using existing drugs, such as rifampin, levofloxacin, and linezolid. In addition, NIAID and other scientists are evaluating two medical imaging technologies, positron emission tomography and computed tomography, for their utility in predicting TB drug treatment outcomes by allowing researchers to monitor whether bacteria remain in the lungs after therapy. These technologies could be used in combination to help facilitate and shorten clinical trials for new drug treatments. Studies to further develop these technologies are currently underway in South Africa.

¹ <http://www.gao.gov/assets/680/673276.pdf>.

In addition to supporting research on TB therapeutics, NIAID is pursuing TB vaccine development to improve upon existing TB vaccine options. NIAID-supported research has contributed to ten of the TB vaccine candidates currently in clinical trials, and NIAID is supporting preclinical development of additional promising vaccine candidates. For example, NIAID supported early-stage development of vaccine candidates H56 and ID93. In addition to protecting against infection, these TB vaccine candidates may also be effective in protecting individuals with latent TB infection from developing active TB disease. These vaccines are currently in clinical development.

Longstanding NIAID investments in TB research and collaboration with domestic and international partners have advanced the development of novel therapeutics and vaccine candidates. NIAID remains committed to combating TB and will continue to support basic, translational, and clinical research focused on developing new countermeasures for drug-susceptible and drug-resistant TB.

DEPARTMENT OF DEFENSE BRAIN BANK

Question. The Department of Defense and the NIH partnered to create the world's first human brain tissue repository for military personnel. However, it is my understanding that NIH researchers are having issues accessing post-mortem tissues from servicemembers affected by blast injury. Dr. Koroshetz, are NIH researchers being provided access?

What are the hurdles you are facing to gain access to these resources?

Answer. It is our understanding that the major hurdle is the absence of an effective manner to obtain informed consent from a service member's family that would allow a careful examination of tissue removed at autopsy by the DOD Medical examiners. DOD currently classifies a careful examination of brain tissue for the effects of blast injury as research, which requires informed consent. It is our understanding that autopsies have been performed at the Office of the Armed Forces Medical Examiner in Dover, Delaware, and that brain tissue was removed but is not available for detailed study due to the lack of a means to obtain consent for study. Although consent is a sensitive and highly personal decision, we believe many families would recognize the potential of such examinations to benefit other current and future service members. DOD has recognized and understood the issues concerning service member brain donation for research purposes, and is working to increase the availability of specimens while also complying with established law and policy governing human subjects research and respecting the needs of families who have recently lost a loved one.

Based on the examination of the handful of well-studied cases, we are concerned that blast injury causes a unique type of brain injury. To know how common these unique findings are requires examination of a larger number of brains. If these findings can be substantiated it would shift the focus to brain imaging evaluations of living veterans who were exposed to blast and would also help to direct valuable research focused on means to protect future service members from blast-induced brain injury.

Question. Can you discuss the importance of having access to brains that have experienced blast injuries?

Answer. Access to brains that have sustained a blast injury is absolutely essential to understand the effects of blast injury. DOD and academic laboratories are studying the effects of blast on animals, and scientists are modeling its effects on the brain with computer simulations. However, these studies are not informed by what actually occurs in human brains that have been exposed to blast. The physical forces from a blast differ in crucial ways from other types of trauma that have been studied in human brains, and the human brain is unique in many ways—for example, the much larger size of the human brain, and especially the cerebral cortex, compared to animals can substantially change the physical forces on brain tissue from blast injury. The unique findings seen in the few well-studied cases, if substantiated, suggest that a change in focus is appropriate.

Question. What do you think researchers will learn if they have access to brains that have sustained a blast injury?

Answer. Based upon examination of brain tissue from the handful of cases, we are concerned that blast injury damages the brain in unique ways, compared to other types of trauma. Understanding the unique pathology is essential to develop better ways to diagnose and treat service members exposed to blast injury and to improve protective measures. For instance, it is an open question as to whether neuropsychiatric disorders classified as PTSD, or even suicide itself may be related to chronic effects of neurotrauma. Brain examination is currently the only means to pursue these questions at this time. The most urgent question is to understand

the incidence and pattern of blast injury in brain tissue and to link the pathologic findings to the service members' medical histories.

ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES INITIATIVE

Question. ECHO is proposing to use existing cohorts as a critical aspect of understanding child health and allow researchers to get a better understanding of the normal trajectory of child development.

Have you selected any cohorts yet? Will the array of cohorts include broad population samples?

Answer. The Environmental influences on Child Health Outcomes (ECHO) program will leverage existing resources to investigate the longitudinal impact of early childhood environmental exposures (e.g., physical, chemical, biological, social, behavioral, natural and built environments) on pediatric development and health outcomes with high public health impact. One specific component of ECHO—the IDEa States Pediatric Clinical Trials Network (ISPCTN)—will leverage the infrastructure at existing IDEa State centers by embedding clinical trials experts at IDEa State locations, facilitating their partnership with other academic institutions.² This national pediatric research network may also help address access gaps for rural and medically underserved children.

NIH recognizes the importance of robust recruitment plans that can address racial and ethnic minority health issues reflective of the needs of the U.S. population. When making awards, NIH will strive for a balance between a robust characterization of environmental factors, including consideration of geographic diversity, and health-related endpoints. Additionally, the ECHO program aims to utilize both large studies to build a repository on the trajectory of healthy development over childhood (health controls), and small, selective studies to address interesting targeted questions that are specific to a disease or have a high-risk population.

Last fall, seven Funding Opportunity Announcements (FOAs) were released to solicit applications for the ECHO program. The applications were due on April 15, 2016 and will be reviewed this summer. Awards are anticipated to be made in September 2016; therefore, no specific cohorts have been selected for funding as of yet. Any investigator with an existing relevant cohort, whether it is supported by the NIH or not, was encouraged to apply.

Question. Are you working with National Center for Health Statistics to ensure ECHO cohorts include measures that would allow you to compare subjects to studies such as the National Health and Nutrition Examination Survey?

Answer. A major feature of the ECHO program is the sharing and harmonization of data across all of the cohorts. Standardized core data elements will be addressed across all studies: demographics; typical early health and development; genetic influences on early childhood health and development; environmental factors; and Patient/Person (parent and child) Reported Outcomes (PROs). During the planning phase, the ECHO Steering Committee, which will be composed of the principal investigators of the ECHO projects, cores and centers, the ECHO ISPCTN, and the NIH ECHO Program Director and staff, and the External Scientific Board, composed of external experts, will develop and provide valuable input on standardizing the collection of the core data elements. They will be strongly encouraged to consider how NHANES, NHIS, and other national surveys can inform the development of these standardized core data elements, and consider how the ECHO data could be compared to known national samples. Additionally, the Children's Health Exposure Analysis Resource (CHEAR) is a network of laboratory hubs that provides researchers access to comprehensive laboratory and data analysis services to measure environmental exposures. CHEAR is expected to become operational in the summer of 2016, and will have the capability of measuring the majority of targeted analytes CDC measures for NHANES, as well as others. The ECHO program is leveraging this existing resource to analyze personal environmental exposures from existing and prospective ECHO sample collections. Therefore, researchers should be able to compare much of the data generated from ECHO with that of other large studies.

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

CANCER MOONSHOT

Question. Dr. Collins, I am curious of the role that the President's cancer "moonshot" initiative will play in the research specifically for childhood cancer. Currently, childhood cancer is the number one disease killer of children under 15 years old and

² <https://www.nigms.nih.gov/Research/CRCB/IDEa>.

the incidence of childhood cancer has increased each year for the past 25 years. In addition, over the past 8 years, less than 4 percent of the National Cancer Institute's (NCI) annual appropriations have been allocated towards pediatric cancer. I understand the budget constraint's many of the institutes are under, however, can you explain why the NCI is not allocating more of its current resources towards childhood cancer initiatives given the statistics?

Answer. The National Cancer Moonshot Initiative is an important opportunity to speed progress on childhood cancers. Not only is childhood cancer research one of the seven core elements within the initiative, several other elements are also important to advancing progress for children with cancer. Other Moonshot elements that are particularly relevant include:

- extending early successes in immunotherapy for cancer treatment (for adults and children)
- building an even greater understanding of cancer genomics—the genetic changes that occur within the cancer cell and in surrounding and immune cells responding to the cancer
- building expanded data sharing systems to speed discovery and verify treatment response for children and adults.

Cancer in children poses unique challenges. Childhood cancers generally possess many fewer mutations than adult cancers and are less likely to have activation of enzymes known as kinases, which are the most frequent targets of cancer drugs for adult tumors. The molecular changes that drive many childhood cancers arise in transcription factors and other cellular targets that are often considered “undruggable.” However, new technologies, built upon advances in chemistry that allow the preparation of libraries of small chemical molecules with a much more complex arrangement of molecular shapes, offer the promise of identifying therapies with the potential to target the unique molecular changes found in pediatric cancers. The National Cancer Moonshot Initiative aims to support research such as this to deliver advances and new treatments for pediatric cancers.

As part of the fiscal year 2017 Moonshot initiative, NCI will also intensify efforts to collect and analyze tumor specimens from the rarest childhood cancers, and NCI will enlist the pediatric oncology community to join in this effort. NCI also expects to build a clinical database focused on the course of rare pediatric cancers that will be widely accessible and will support further productive research that can lead to new cancer treatments.

The National Cancer Moonshot Initiative's Blue Ribbon Panel and its working groups will continue to identify specific promising research opportunities for each element of the initiative, including childhood cancer research. The Blue Ribbon Panel includes a number of cancer researchers with pediatric cancer expertise, such as Dr. James Downing, President and CEO, St. Jude Children's Research Hospital, and Dr. Peter Adamson, Director of Experimental Therapeutics in Oncology at the Children's Hospital of Philadelphia. Dr. Adamson is also Chair of the NCI-supported Children's Oncology Group, and a member of the National Cancer Advisory Board.

In addition to the Blue Ribbon Panel and its working groups, the initiative is also seeking feedback from across the cancer research and advocacy communities regarding all areas of research focus, including childhood cancer research.³ Additional information about the National Cancer Moonshot Initiative, including childhood cancer research within the initiative, can be found at the NCI website.⁴

New Childhood Cancer Research Initiatives

NCI is also supporting new research opportunities specific to childhood cancer, including a Pediatric Provocative Questions Initiative and the Pediatric MATCH precision medicine trial. NCI is eager to accelerate progress in cancer research by attempting to define potentially game-changing scientific questions that could influence the directions taken by NCI-sponsored research in the future. The NCI Provocative Questions Initiative is designed to encourage research around some of the most challenging scientific questions while engaging the scientific community in serious debate in an effort to identify compelling research opportunities.

NCI held two childhood cancer Provocative Questions workshops in 2015 to identify questions that address gaps in the pediatric oncology research field. NCI plans to release the pediatric oncology provocative questions this spring through program announcements designed to generate innovative approaches to address childhood cancer research challenges.

³The public and research communities are invited to submit ideas at this website: <https://cancerresearchideas.cancer.gov/>.

⁴<http://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative>.

The Pediatric MATCH precision medicine trial will provide a tremendous opportunity to test molecularly targeted therapies in children with advanced cancers who have few other treatment options. With the genomic data captured in the trial, it will also produce an invaluable resource for studying the genetic basis for why some pediatric cancers progress or recur while others do not. As in the adult NCI-MATCH trial, DNA sequencing will be used to identify children whose tumors have a genetic abnormality for which either an approved or investigational targeted therapy exists. Pediatric MATCH, which will be led by the NCI-funded Children's Oncology Group, is under development and is expected to launch in late 2016.

Other NCI Support for Childhood Cancer Research

NCI has prioritized the development of new treatments for pediatric cancer in the NCI Experimental Therapeutics (NExT) Program.⁵ This program focuses on advancing breakthrough discoveries in basic and clinical research into new therapies, and several new inhibitors with potential to treat pediatric cancer are being studied for this purpose. There are currently nine agents from the NExT program being studied in pediatric clinical trials. Two examples of these include the investigational agent ganitumab for Ewing sarcoma and the FDA-approved dinutuximab (ch14.18) therapy for high-risk neuroblastoma.

NCI's active role in developing these agents is what has made these trials possible. The development of ganitumab was halted by the pharmaceutical industry after negative results in studies for adult cancers, and NCI acquired the agent from the industry sponsor to continue development for therapy for Ewing sarcoma. Similarly, NCI supported the development of dinutuximab for high-risk neuroblastoma for decades, from early funding for investigator-initiated research, to manufacturing and sponsoring the Phase III trial that led to dinutuximab's approval by FDA, and finally to the NCI Cooperative Research and Development Agreement (CRADA) with United Therapeutics that brought this drug to market for patients.

As noted above, childhood cancers pose unique scientific challenges and opportunities. NCI is supporting research to address these challenges in ways that can lead to better outcomes for children with cancer. This is a high priority research area for NCI, and we are urging the oncology community to submit creative research proposals focused on childhood cancers. NCI continues to support the best research opportunities to identify promising new therapies, improve the outlook for cancer survivors, and to support the foundation of basic research needed to achieve these goals.

The funding figures cited in your question reflect only research projects identified as specifically focused on childhood cancer in a given fiscal year, such as the research data reported in the NIH Research, Condition, and Disease Categorization (RCDC) database.⁶ While RCDC is a useful tool, it does not provide the complete picture of NIH and NCI investments that are critical to advancing childhood cancer research. For example, approximately half of the NCI budget—and half of the overall NIH budget—supports basic research that may not be specific to one type of cancer. By its nature, basic research cuts across many disease areas and makes important contributions to our knowledge of the underlying biology of cancer. This knowledge supports the ability of the research community to make advances against many cancer types.

Over the years, research in childhood cancers has led to important advances for adults with cancer. Similarly, research focused on adult cancers has led to progress for children with cancer. We have also demonstrated that research focusing on a particular type of cancer has led to advances across many cancer types. For these reasons, the funding levels reported in RCDC and other systems do not definitively capture all research relevant to a given category.

In addition to soliciting applications in areas of scientific focus, NCI also remains committed to supporting a number of key research efforts focused specifically on childhood cancers. NCI has been renewing many of these programs for numerous 5-year funding periods. Examples of these critical long-term investments in childhood cancer research include:

- The Children's Oncology Group (COG), which is part of NCI's National Clinical Trials Network (NCTN), develops and coordinates pediatric cancer clinical trials that are available at more than 200 member institutions, including cancer centers throughout the United States and Canada.⁷ In addition to conducting traditional late-phase clinical trials, the COG has established a Phase 1 and Pilot Consortium that is separately funded by NCI to conduct early-phase trials and

⁵ <http://next.cancer.gov/about/mission.htm>.

⁶ https://report.nih.gov/categorical_spending.aspx.

⁷ <https://www.childrensoncologygroup.org/>.

pilot studies so new anticancer agents can be rapidly and efficiently introduced into pediatric cancer care.⁸

- The Pediatric Preclinical Testing Consortium (PPTC) systematically evaluates new agents in genomically characterized childhood cancer solid tumor and leukemia in vivo models.⁹ The primary goal of the PPTC is to develop high-quality preclinical data to help pediatric oncology researchers identify agents that are most likely to show significant anticancer activity when tested in the clinic against selected childhood cancers.
- The Childhood Cancer Survivor Study (CCSS) is studying the long-term effects of cancer and cancer therapy on approximately 35,000 survivors of childhood cancer who were diagnosed between 1970 and 1999.¹⁰ NCI has supported CCSS since its launch in 1994. NCI has also recently supported a complementary effort, the St. Jude Lifetime Cohort Study, which will allow for replication of findings from genomic studies and the development of collaborative projects to refine risk-based follow-up guidelines and improve outcomes among childhood cancer survivors.¹¹
- The Pediatric Brain Tumor Consortium was formed by NCI in 1999 as a multidisciplinary cooperative research organization devoted to identifying superior treatment strategies for children with primary brain tumors.¹² The participating academic centers and children's hospitals are responsible for the diagnosis and treatment of the majority of children with primary brain tumors in the United States. PBTC has a direct working relationship with the Children's Oncology Group (COG) to ensure that results from Phase I and II trials can be confirmed through additional Phase II and multi-agent Phase III clinical trials in the COG.
- The Pediatric Oncology Branch (POB) in NCI's Center for Cancer Research, part of NCI's intramural research program, conducts high-risk, high-impact basic, translational, and clinical research dedicated to the study and treatment of childhood cancers.¹³

QUESTIONS SUBMITTED BY SENATOR THAD COCHRAN

PEDIATRIC CLINICAL TRIALS NETWORK

Question. I am pleased that the NIH has shown a commitment to including IDeA States in the Pediatric Clinical Trials Network. It is my understanding that the network will focus on environmental influenced diseases like asthma, obesity, and prematurity, all of which are all too prevalent in my State of Mississippi. The current program announcement from NIH provides for grants to fund necessary infrastructure for clinical trials research sites and to promote career development for pediatric clinical researchers. Please provide me with more information about how this network will function as it moves forward. In particular, what studies will the network perform? How will the studies be chosen, and how will they be funded?

Answer. NIH released a series of funding opportunity announcements (FOAs) on December 7, 2015 to establish the Environmental Influences on Child Health Outcomes (ECHO) program. The ECHO program has been designed to investigate the longitudinal impact of pre-, peri-, and postnatal environmental exposures on pediatric health outcomes with high public health impact. The IDeA States Pediatric Clinical Trials Network (ISPCTN) has been developed as a component of the ECHO program and includes two FOAs: The Clinical Sites for the IDeA States Pediatric Clinical Trials Network (RFA-OD-10-001), and the Data Coordinating and Operations Center for the IDeA States Pediatric Clinical Trials Network (RFA-OD-16-002). ISPCTN is being established to provide an opportunity to children in rural and medically underserved locations in IDeA States to participate in state-of-the-art clinical trials, to enhance pediatric clinical trial capacity at State and national level, and to facilitate the implementation of well-designed clinical trials in pediatric populations.

How will the ISPCTN coordinate with the ECHO program as a whole? ISPCTN will study any disease or condition relevant to the pediatric population, but priority will be given to the four focus areas of the ECHO program including: upper and

⁸ <https://www.childrensoncologygroup.org/index.php/phase-1-home>.

⁹ http://ctep.cancer.gov/MajorInitiatives/Pediatric_Preclinical_Testing_Program.htm.

¹⁰ <http://www.cancer.gov/cancertopics/types/childhoodcancers/ccss>.

¹¹ <https://www.stjude.org/research/clinical-trials/sjlifelong-term-effects.html?vgnextoid=1c4303fb30c23110VgnVCM1000001e0215acRCD>.

¹² <https://www.pbtc.org/>.

¹³ <https://ccr.cancer.gov/pediatric-oncology-branch>.

lower airway diseases; obesity; pre-, peri-, and postnatal outcomes; and neurodevelopment. All prospective data collection will be encouraged to utilize the ECHO program's Core Elements and standardized research measures. Structurally, there will be representatives of the ISPCTN on the ECHO Steering Committee and subcommittees.

How will this network function and move forward? The overall framework will consist of dedicated pediatric clinical teams at participating institutions, a professional development component, and a central Data Coordinating and Operations Center (DCOC). The institutions that will successfully compete to become IDEa State Pediatric Clinical Sites will be integrated with the DCOC to form a Research Network to conduct multicenter studies of pediatric conditions and disease processes. The proposed activities will provide the infrastructure and resources needed to initiate and participate in pediatric clinical trials and enhance the competitiveness of the investigators to obtain funding for pediatric clinical research.

DCOC will provide comprehensive services across the network. DCOC will have primary responsibility for resource allocation, data management and analysis, and data sharing for research conducted through the network in collaboration with the ISPCTN Steering Committee, the ECHO Steering Committee, and the NIH Program Staff. DCOC will facilitate and establish collaborations within the network and outside of the network, will develop and implement quality control measures, establish and maintain human subject protections oversight, develop a central IRB, implement relevant professional development programs, and organize and implement monitoring activities. ISPCTN will be directed by a Steering Committee with standing committees and sub-committees; a Scientific Oversight Board and a Data Safety Monitoring Board will be constituted as well. ISPCTN will also be guided by the ECHO Steering Committee and External Scientific Board. Each clinical site will have a dedicated pediatric clinical trial team including a board certified Pediatrician as a Principal Investigator (PI), a Research Nurse Coordinator, and a Data Manager, who will implement the studies.

How will the studies be chosen? ISPCTN will primarily function to augment pediatric clinical trials initiated by other entities to improve access to state-of-the-art pediatric clinical trials to populations who would otherwise not have access to them. Studies initiated within the network will also be encouraged. The ECHO Program Officials and the NIH Project Scientists, one from NICHD and one from NIGMS, will assist the PI(s) and Program Directors of the Clinical Sites and the DCOC of ISPCTN to identify research topics of high priority and provide guidance for the implementation of the protocols appropriate for the network goals and objectives. Interested investigators will contact DCOC as a clearing house to determine feasibility and network interest. Clinical trials to be conducted through the network will require approval by the ISPCTN Steering Committee in conjunction with the NIH ECHO Program Officials.

How will the studies be funded? All the studies will be funded by DCOC. DCOC will receive its entire budget when the award is made, and will allocate \$4.53 million per year for each of the 4 years of the program budget period in direct costs to pay for services. These costs will be distributed to the Clinical Sites and for necessary monitoring, DSMB visits, and Scientific Oversight Board activities.

HIV/AIDS VACCINE

Question. I understand that the NIH is on the path toward discovering a vaccine for HIV/AIDS. What is the Administration's position on funding for this effort? How much of the request will be devoted to HIV/AIDS vaccine discovery? Why do you believe that is sufficient?

Answer. The fiscal year 2017 President's Budget requested \$554 million for HIV vaccine research at NIH. Development of an HIV vaccine would represent a significant public health achievement and provide populations around the world with a safe and effective tool for preventing HIV infection.

The National Institute of Allergy and Infectious Diseases (NIAID) is the lead NIH Institute for research on HIV/AIDS, including research to develop an effective vaccine. NIAID oversees a robust portfolio of basic, translational, and clinical research on HIV/AIDS with the goal of successfully ending the HIV/AIDS pandemic. While significant progress has been made in combating HIV/AIDS through the implementation of prevention and treatment strategies supported by NIAID research, the development of a safe and effective HIV vaccine is critical to achieve a durable end to the HIV/AIDS pandemic and thus remains a top priority for NIAID.

NIAID supports a comprehensive program of extramural and intramural HIV vaccine research, including at the NIAID Vaccine Research Center (VRC). Investigators are working at all stages of the vaccine development pipeline to design, develop, and

test vaccine candidates to prevent HIV infection. To date, NIAID has supported 148 vaccine trials to evaluate 109 vaccine products and 27 adjuvants—vaccine additives designed to boost the immune response to vaccination.

HIV vaccine development supported by NIH builds upon basic research that illuminates the mechanisms of HIV pathogenesis. Studies of viral and host factors involved in host immune responses to HIV will contribute knowledge that can help researchers develop novel vaccine strategies. For example, VRC scientists discovered VRC01, a broadly neutralizing antibody that is capable of inhibiting a number of HIV strains. Phase I studies are currently underway to evaluate the safety and immunogenicity of VRC01. In addition, Phase IIb studies initiated in March 2016 are evaluating the ability of infusions of VRC01 to prevent HIV infection. Understanding the preventive properties of broadly neutralizing antibodies will help scientists design more effective HIV vaccines that aim to inhibit multiple strains of HIV.

NIAID is collaborating with the Pox-Protein Public-Private Partnership (P5) to confirm and extend results of the RV144 clinical trial in Thailand. This trial was the first study to demonstrate moderate protection against HIV infection in people who received a candidate HIV vaccine regimen. To build upon the results of the RV144 trial, NIAID launched the HVTN 100 Phase I/II clinical trial in South Africa. This trial is evaluating an investigational vaccine regimen that was designed to improve upon the efficacy of the vaccine regimen used in the RV144 trial. If the vaccine is found to be safe and adequately immunogenic, NIAID and collaborators anticipate launching a follow-up randomized controlled trial, HVTN 702, in late 2016 to test the regimen's protective efficacy.

In addition to HIV vaccine research, NIAID is supporting research to optimize existing strategies and to develop new strategies for HIV treatment and prevention, as well as to explore novel approaches to curing HIV. In partnership with scientific and community stakeholders, NIAID-supported research is advancing progress toward an AIDS-free generation, including through critical work to develop an effective HIV vaccine.

UPDATING RESEARCH CENTERS IN MINORITY INSTITUTIONS GUIDELINES

Question. The Research Centers in Minority Institutions (RCMI) program has proven important in building biomedical research capacity at Historically Black Colleges and Universities (HBCUs) nationwide, including at Jackson State University in my State. I understand the National Institute on Minority Health and Health Disparities is preparing updated guidelines for the RCMI program. Where is NIMHD in that process? How will eligibility for the RCMI program change? For example, will non-minority institutions become eligible for RCMI funding, or will institutions that have received “significant amounts of Federal funding” now be allowed to compete? Will the purposes and uses of the funds change? If yes, how so? It is my hope that this program will continue to provide important capacity-building funds to minority-serving institutions like Jackson State.

Answer. Since the transfer of the Research Centers in Minority Institutions (RCMI) program to the National Institute on Minority Health and Health Disparities (NIMHD) in 2012 with the dissolution of the National Center for Research Resources (NCRR), NIMHD has made it a priority to integrate the RCMI program into the existing NIMHD portfolio. NIMHD has focused on specific programmatic goals and objectives in order to minimize overlap and maximize the scientific benefit of the Federal resources and plans to provide updated guidance to the extramural research community in the summer of 2016. NIMHD is committed to keep the intent of the RCMI program and will continue to engage institutions with a history of supporting students and trainees underrepresented in biomedical research and to serving diverse populations.

Consistent with the intent of the RCMI program, the priority continues to be strengthening the research environment at the institution. There are multiple ways to accomplish that goal, from providing specialized expertise such as biostatistics, health informatics or specific research skills in laboratory science, to conducting specific research projects in minority health or health disparities. Individual RCMI institutions have and will continue to be able to focus on different scientific areas including basic biomedical, behavioral, and/or clinical research that best align with the strengths of their institution.

NIH “MARCH-IN RIGHTS”

Question. What is your position on the use of NIH’s “march-in-rights” as a price control measure?

Answer. NIH shares the public's concern about any individuals who need medical treatments may be prevented access to treatment on the basis of the cost. Some have suggested that NIH utilize the Bayh-Dole march-in authority as a means of addressing the difficult situation with drug pricing. The Bayh-Dole Act, however, does not appear to have been designed to address situations where the price is the obstacle for access to products utilizing Government-funded inventions. The Act seems to address the circumstances where the products are not available because they are not being commercialized and have not entered the market. Another case for using march-in may occur when serious public health needs are not being reasonably met by the owner of the patent or the company selling the product. In such cases, NIH has the authority to utilize the march-in authority. NIH reviews each request for the use of march-in on case by case basis. In previous cases where requests were based on drug pricing issues, NIH did not find that the march-in statutory criteria were met.

COMBATTING ANTIBIOTIC RESISTANT BACTERIA INITIATIVE

Question. Through the Combatting Antibiotic Resistant Bacteria initiative, the FDA and the CDC have recognized that antibiotic resistance is a growing public health concern worldwide. As part of this effort, the White House issued a National Action Plan for Combatting Antibiotic-Resistant Bacteria in 2015. In January, the NIH announced that approximately \$5 million in funding was granted to research projects to develop non-traditional therapeutics for bacterial infections to help address the growing health threat of antibiotic resistance. Does NIH have adequate resources to address this growing threat?

Answer. Research to address antibacterial-resistant pathogens is a top priority for the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH Institute for research on infectious diseases. NIAID plays an important role in the President's National Strategy for Combating Antibiotic-Resistant Bacteria (CARB) by investing in basic, translational, and clinical research on antibacterial resistance. The additional \$100 million provided by the Congress in the fiscal year 2016 Consolidated Appropriations Act to address antibacterial research and development is both timely and vital to address the growing problem of antibiotic resistance. This funding will bolster and expand NIAID's research efforts to better understand and combat antibacterial resistant infections.

In accordance with the objectives outlined in the National Strategy for CARB, NIAID is currently sequencing bacterial strains for the National Database of Resistant Pathogens; optimizing current treatment strategies to reduce the emergence of drug resistance; and developing diagnostic platforms capable of detecting multiple resistant pathogens. NIH is partnering with the Biomedical Advanced Research and Development Authority, with assistance from FDA and CDC, to incentivize diagnostic research by designing a prize competition for the development of a rapid, point-of-care diagnostic test for healthcare providers. NIAID also is expanding and strengthening its clinical research efforts, including through the NIAID Antibacterial Resistance Leadership Group (ARLG), to facilitate high-priority research on antibacterial resistance. For example, the ARLG is currently investigating the use of shortened courses of antibiotics in pediatric populations in an effort to enhance antibiotic stewardship and infection control.

Consistent with the CARB objectives, the NIAID initiative Non-Traditional Therapeutics that Limit Antibacterial Resistance supports early-stage, translational research projects focused on discovery and development of non-traditional therapeutics that provide alternative treatment strategies for infected patients. In January 2016, NIAID awarded approximately \$5 million in funding for 24 research projects seeking to develop non-traditional therapeutics for bacterial infections, including *Clostridium difficile*, *Staphylococcus aureus*, and carbapenem-resistant Enterobacteriaceae (such as *Klebsiella pneumoniae*).

In addition, NIAID continues to support the discovery and development of new therapeutics for Gram-negative pathogens, such as biofilm inhibitors, and anti-virulence, immune-based, and adjunctive therapies. To that end, in 2016, NIAID will make multiple awards under several other research initiatives that are designed to advance the development of new therapeutic products and approaches aimed at addressing drug resistance. These initiatives include Partnerships for the Development of Host-Targeted Therapeutics to Limit Antibacterial Resistance and Systems Biology and Antibacterial Resistance. NIAID also will fund new contracts to support the development and early clinical evaluation of promising lead therapeutic candidates and products that demonstrate broad spectrum therapeutic activity, including activity against antibiotic-resistant bacteria.

NIAID has provided support for at least 25 percent of antibiotics currently in clinical development. Currently, NIAID is supporting several clinical trials evaluating new ways to treat gonorrhea, including a Phase II trial of an oral antibiotic AZD0914 developed by AstraZeneca; a Phase I trial assessing the pharmacokinetics of a next-generation macrolide antibiotic, solithromycin; and a Phase III trial comparing solithromycin to standard of care treatment for gonorrhea. NIAID also is supporting trials to determine optimal antibiotic treatment (e.g., dosage, duration) using existing off-patent antibiotics for a variety of infections, including community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections; staphylococcal bacteremia; Gram-negative bacteremia; acute otitis media; urinary tract infections; and hospital-acquired pneumonia.

NIAID remains committed to conducting and supporting research on antimicrobial resistance, including the development of rapid, point-of-care diagnostics, improved and innovative therapies, and vaccines to prevent infections. Utilizing additional resources provided by the Congress in fiscal year 2016, NIAID will continue to enhance partnerships with industry, academia, and other Federal Government agencies to support the goals of the National Strategy for CARB.

ANIMAL RESEARCH

Question. Great strides in medical research and treatment have come from the study of animal models. Whether a scientist is studying kidney failure or drug addiction, there is clear value in translating the lessons learned to the human population. Some in the industry have suggested that NIH may be backing away from its longstanding commitment to study certain species of animals due to pressure from activists. What is your intention related to animal research? How will you ensure that the humane and scientifically-justified use of animal models is permitted for those using NIH funds to support their research?

Answer. NIH is committed to funding the most meritorious research projects, including those involving animal model(s). Research involving vertebrate animals is key to helping us understand and improve human health in a multitude of ways, including the development of treatments and interventions. For ethical reasons, these studies cannot be carried out in humans and require the use of animal studies to understand fundamental biological systems. Ultimately, these findings assist researchers in identifying potential treatments and interventions by helping to elucidate the mechanisms underlying health and disease.

Figure 1 shows the success rates for new, competing R01 grant applications over the past 5 fiscal years, broken out by whether the application proposes only vertebrate animal research, only human subjects research, both vertebrate animal and human subjects research, or neither. The R01 grant is NIH's most commonly used funding mechanism and is used to support a majority of NIH's basic research portfolio. Success rates for studies involving only vertebrate animals and those involving both vertebrate animals and human subjects have increased in fiscal years 2014 and 2015, showing NIH's continued commitment to funding meritorious research using vertebrate animal models.

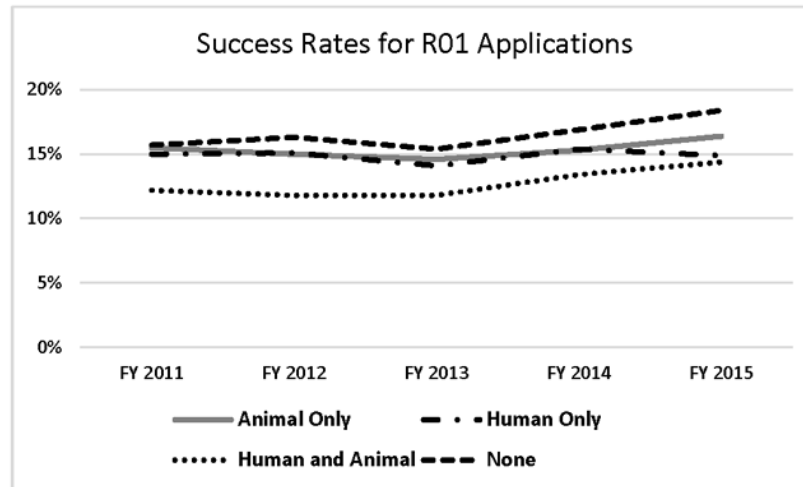


FIGURE 1. Success rates for competing R01 applications, by type of research proposed, over the past 5 fiscal years.

NIH takes animal welfare seriously, and has numerous policies and protocols in place to assure the ethical treatment and use of these invaluable resources. The agency remains confident that the oversight framework for the use of vertebrate animals in research is robust and has provided sufficient protections to date. NIH will continue to support the meritorious research proposals using vertebrate animals, so long as the research satisfies ethical principles of scientific rigor, appropriateness of the model, and consideration of animal welfare. Moreover, NIH has the necessary mechanisms to implement these relevant policies to ensure the continued responsible use of vertebrate animals in biomedical and behavioral research.

IDEA PROGRAM

Question. I know you are aware of how the IDeA program has helped build biomedical research capacity across the Nation. The fiscal year 2016 omnibus provided additional funds, reflecting Congress's continued support for this program. What are your plans for the IDeA programs going forward? What are some particular success stories that have come from IDeA investments?

What are your plans for the IDeA programs going forward?

Answer. NIGMS foresees the IDeA Program as a long-term interventional capacity-building program targeting States and jurisdictions that have consistently trailed in obtaining significant NIH support. The intent is to transform institutions with infrastructure, human resource, and economic challenges to become more competitive biomedical research enterprises through various distinct but complementary initiatives.

Currently, institutions in 23 States and Puerto Rico are eligible for funding from the IDeA Program.¹⁴ For fiscal year 2017 and in the foreseeable future, the IDeA program will continue to support investigators in eligible States through the following initiatives:

—*IDEA Networks of Biomedical Research Excellence (INBRE).*—The INBRE initiative enhances, extends, and strengthens the research capabilities of biomedical research faculty in IDeA States through a statewide program that links a research-intensive institution with primarily undergraduate institutions. INBRE supports institutional research and infrastructure development; research by faculty, postdoctoral scientists and students at participating institutions; and outreach to build science and technology knowledge in the States' workforces. Only one award is made per eligible State. Currently (fiscal year 2016), NIGMS sup-

¹⁴ Alaska, Arkansas, Delaware, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Maine, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Oklahoma, Rhode Island, South Carolina, South Dakota, Vermont, West Virginia, Wyoming.

ports 24 INBRE awards. For fiscal year 2017, NIGMS anticipates continuing support for these 24 INBRE awards.

—*Centers of Biomedical Research Excellence (COBRE—Phases I, II, and III).*—The goal of the COBRE initiative is to strengthen institutional biomedical research capabilities in IDeA States through three 5-year phases of infrastructure and faculty development of thematic and multidisciplinary research centers. In fiscal year 2015, NIGMS supported 107 COBRE awards. For the current year (fiscal year 2016), 12 new Phase I COBRE grants will be awarded. In fiscal year 2017, NIGMS will support non-competing awards and continue to hold open competitions for new and continuing COBRE awards.

—*IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR).*—The IDeA-CTR initiative develops network infrastructure and capacity in eligible States to conduct clinical and translational research focused on health concerns that affect medically underserved populations and/or that are prevalent in IDeA States. IDeA-CTR awards support mentoring and career development activities in clinical and translational research. In fiscal year 2015, NIGMS supported 3 IDeA-CTR awards. In the current year (fiscal year 2016), 4 new IDeA-CTR awards will be made. In fiscal year 2017, NIGMS will support non-competing awards and continue to hold open competitions for new and continuing IDeA-CTR awards.

—*Research Co-Funding.*—IDeA co-funding is provided to eligible applications that have already been judged meritorious by NIH peer-review committees and national advisory councils but are outside the range of applications under consideration for funding by the other NIH Institutes and Centers (ICs). In fiscal year 2015, IDeA co-funded 25 R01/R15 awards to 18 NIH ICs. For the current year (fiscal year 2016), \$9 Million is allocated for the co-funding initiative. In fiscal year 2017, NIGMS anticipates to continue soliciting applications from other ICs for co-funding.

—*Administrative Supplements.*—Based on continuing evaluation of the IDeA program, NIGMS will occasionally solicit applications for administrative supplements from current grantees in order to address emerging areas for development or enhancement. For the current year (fiscal year 2016), the Institute published an administrative supplement solicitation for the optimization and/or consolidation of core facilities supported by the IDeA program. The projected budget for this initiative in fiscal year 2016 is \$8 Million.

Additionally, for fiscal year 2017, the IDeA program will provide continuing support for the non-competing INBRE, COBRE, and IDeA-CTR awards; these awards constitute the IDeA program budget base. As indicated above, the rest of the IDeA program budget will support new competing COBRE and IDeA-CTR awards, and co-funding of meritorious applications from other ICs.

Question. What are some particular success stories that have come from IDeA investments?

Answer. Investigators in a COBRE at the University of Mississippi that is focused on finding natural products that affect neurological processes (Principal Investigator: Steve Cutler) are developing melt-cast films for the efficient and prolonged topical delivery of therapeutic small molecules to the posterior segment of the eyes. Diseases affecting the posterior segment of the eye such as diabetic retinopathy, age related macular degeneration, diabetic macular edema and proliferative vitreo-retinopathy are some of the major causes of blindness in the United States. Treating posterior segment eye diseases has always been a great challenge because of the unique physiological and anatomical barriers of the eye. In a recent publication from this group, the COBRE investigators demonstrated that melt-cast films based on polyethylene oxide N10 can serve as a viable platform for sustained topical delivery of therapeutic agents into tissues in the back of the eye.

Jennifer Sasser, a COBRE-supported junior investigator at the University of Mississippi Medical Center, characterized a novel model of the pregnancy-related disease superimposed preeclampsia. This new model of the disease in rats provides a powerful tool to gain a greater understanding of the pathogenesis of preeclampsia. Preeclampsia is a leading cause of maternal morbidity and mortality worldwide with currently no effective treatments other than delivery of the placenta. The new rat model of preeclampsia allows for the analysis of changes throughout pregnancy in the placenta, vasculature, and kidney, as well as the discovery of new biomarkers that are present early during pregnancy and would allow early detection of the condition. Using this new rat model, Sasser and colleagues found that the phosphodiesterase inhibitor drug, sildenafil, improves the maternal syndrome of preeclampsia as well as blood flow to the fetus and placenta, providing preclinical evidence to support the hypothesis that inhibiting the enzyme phosphodiesterase type 5 may be a therapeutic strategy for the treatment of preeclampsia.

The IDeA Program appropriation has been successfully leveraged by IDeA investigators to provide additional NIH funding to the eligible jurisdictions. For the 8-year period spanning fiscal years 2007–2014, the IDeA Program appropriation totaled \$1.9 billion. Additional NIH funding obtained during this period totaled \$12 billion, close to a 7-fold return in investment.

While the number of COBRE-supported investigators increased modestly during the 8-year period spanning fiscal years 2007–2014, the productivity of the investigators increased significantly. Whereas the number of COBRE-supported investigators increased only 9 percent when comparing fiscal years 2007–2010 (4-year average = 950) to fiscal years 2011–2014 (4-year average = 1,034), the number of COBRE-enabled publications increased 43 percent in the corresponding period [fiscal year 2007–2010 (4-year total = 3,951) vs fiscal year 2011–2014 data (4-year total = 5,651)].

Blake Wiedenheft, a COBRE-supported Assistant Professor at Montana State, has moved beyond IDeA support and is now funded by an NIGMS R01. He was recently invited to give the first Annual NIGMS Director’s Early Career Investigator Lecture. Wiedenheft was honored for his contributions to understanding the three-dimensional structures of key components of the CRISPR-Cas9 gene editing system. Even though he is still early in his career, Wiedenheft has already established himself as one of the international leaders in this field.

In 2014, when Professor Susan Harkema’s research at the University of Louisville in Kentucky was published in the journal *Brain*, it became an overnight sensation and was featured prominently in all the major print and broadcast media outlets. Harkema and her team demonstrated that modulating the spinal circuitry with epidural stimulation enabled completely paralyzed individuals to process conceptual, auditory and visual input to regain relatively fine voluntary control of paralyzed muscles. Harkema conducted the research as one of the project leaders in the Kentucky Spinal Cord Injury Research Center, a COBRE funded by the IDeA program.

A COBRE focused on regeneration medicine based at the Mount Desert Island Biological Laboratory (MDIBL) in Maine has spun off the first company in the Laboratory’s 115-year history, led by the Principal Investigator Kevin Strange and junior investigator Voot Yin. The new company, Novo Biosciences Inc., will look at the therapeutic potential of drugs that speed tissue healing and stimulate the regeneration of lost and damaged body parts. Strange and Yin serve as the CEO and Chief Scientific Officer, respectively, of the new company. Yin, an Assistant Professor at MDIBL, discovered the tissue regenerative effects of an experimental drug in a zebrafish model of regeneration using COBRE funds.

COBRE investigators at the University of Arkansas for Medical Sciences set up telemedicine (TM) capabilities statewide in an effort to improve clinical outcomes for very low birth weight (VLBW) neonates. A prospective study (July 2009 to March 2010) that looked at the availability of TM consultation capabilities and neonatal interventions showed decreased deliveries of VLBW neonates in hospitals without NICUs and was associated with decreased statewide infant mortality. Telemedicine can be an effective way to translate evidence-based medicine into clinical care.

A group of researchers at the University of Arkansas for Medical Sciences (UAMS) have discovered a new molecular “earmark” on DNA that may determine the sex of all mammals. COBRE-supported UAMS biochemist Alan Tackett, professor of Biochemistry and Molecular Biology in the College of Medicine, led a team of researchers that uncovered the earmark, N6-methyladenine, found to regulate access to DNA on the X-chromosome that ultimately determines the sex of mammals. In addition, the research has the potential to uncover new targets for therapeutic development for cancer and other diseases. Their findings were published in the April 2016 issue of the journal *Nature*.

Alayna Caffrey, a doctoral student in Montana State University’s Department of Microbiology and Immunology, published important new findings about how healthy immune systems fight off deadly fungal infections. She was also one of only 10 people selected to present her work at an international scientific conference in Galveston, Texas. Caffrey studies the early immune response against *Aspergillus fumigatus*, a common mold that can be found in soil or compost piles. The mold causes severe lung infections in people with weakened immune systems, such as individuals with leukemia, chemotherapy or organ transplants. To help lower the percentage of deaths and understand what goes wrong in weakened immune systems, Caffrey looked at healthy immune systems to see how they respond to *Aspergillus fumigatus*. She discovered that a molecule called IL-1a is critical for recruiting white blood cells to an infection site. Caffrey conducted the studies in the lab of Josh Obar, a COBRE-supported investigator. The work published in *PLoS Pathogens* was a collaboration between Obar’s group and another COBRE at the Geisel School of Medicine at Dartmouth.

ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

Question. The University of Mississippi Medical Center serves as a field center and conducts research in the NIH's Atherosclerosis Risk in Communities (ARIC) Study, which examines cardiovascular disease in over 15,000 volunteer participants across the country. This original cohort of people who participate in this study enrolled in 1987, so they are well into old age today. What are the NIH's plans for recruiting the adult children of the current ARIC cohort, in the model of the Framingham Heart Study, in order to continue this important research?

Answer. The Atherosclerosis Risk in Communities (ARIC) Study has resulted in outstanding contributions to the understanding of atherosclerosis and cardiovascular disease (CVD) as evidenced by the more than 1,700 publications from the study to date. With almost 30 years of follow-up, the ARIC Study is among the longest-running cohort studies with a large number of African American participants. The ARIC study data on risk factors and incidence rates shows that African Americans are at very high CVD risk.

This long-running multi-site cohort study has produced a number of significant research findings including the following:

- The ARIC Study provided some of the first documentation that diabetes is associated with accelerated cognitive decline.
- Results from the ARIC Study include some of the first evidence for lifestyle factors contributing to risk of venous thromboembolism, offering possible keys to prevention.
- Despite the higher prevalence of hypertension and diabetes in African Americans, the magnitude of the association of these two conditions with CVD is similar to the associations in whites.
- The ARIC Study helped establish that risk of atrial fibrillation is lower in African Americans than whites and that there is a link between obesity and atrial fibrillation.

In 2013, the NHLBI Director charged a working group of our National Heart, Lung, and Blood Advisory Council to consider the future course for CVD epidemiology studies. Published in 2015 (Roger VL et al. *Amer J Epidemiol* 2015), the group's recommendations included "fostering a more open, competitive approach to evaluating large-scale longitudinal epidemiology and population studies." NHLBI is developing a process to fund new and renewed epidemiologic studies that incorporate the recommendations from this working group. One goal is to solicit from investigators, innovative research ideas that leverage existing scientific resources, such as a cohort study of the adult children of the current ARIC study. Using the Framingham Heart Study, which includes three generations of participants, as an example, an offspring cohort of the ARIC study is possible.

ALZHEIMER'S RESEARCH

Question. Last year, this Committee provided a \$350 million increase to funding for Alzheimer's disease research. This additional funding will help researchers, like those at the Memory Impairment and Neurodegenerative Dementia (MIND) Center at the University of Mississippi Medical Center, find a way to alleviate the dreadful symptoms and realities of this heinous disease. Please give us examples of any recent breakthroughs that are a result of investment in Alzheimer's research at the NIH.

Answer. Research on Alzheimer's disease in the United States has benefited from the provision of additional funds in the past several years. Many of the studies that the National Institute on Aging (NIA) and other NIH Institutes supported with these funds are ongoing, and we look forward to reporting on the results as they become available. Most notably, the \$350 million we received in fiscal year 2015 to support Alzheimer's research will fund, among other initiatives, research under 10 Program Announcements soliciting funding applications across the spectrum of Alzheimer's disease research. The initial response to these Program Announcements was extremely robust, and initial awards are anticipated for late fiscal year 2016.

Promising new therapeutics currently in clinical testing include:

- LM11A-31, a compound able to enter the brain and prevent the loss of nerve cells and the connections between them. NIA supported preclinical testing of this compound, and an industry-supported Phase I safety trial in young and in elderly normal subjects showed no significant adverse effects for a wide range of doses. Further human testing is planned.
- BPN14770, which restores function of damaged synapses in the brain. NIA, along with the NIH Blueprint Neurotherapeutics Network, also supported the early development of the compound—which, if effective, may benefit patients

not only with Alzheimer's but with other brain disorders, such as schizophrenia, as well. This compound recently entered Phase I clinical trials.

- Allopregnanolone, a neurosteroid that promotes growth of new neurons and may protect against Alzheimer's pathology. NIA-supported researchers recently concluded a Phase I clinical trial and are currently analyzing the results.

Ongoing initiatives include:

- NIH Accelerating Medicines Partnership (AMP), a joint public-private partnership to identify and validate promising biomarkers of disease. In March, AMP launched its Alzheimer's Big Data Portal and concomitantly released the first wave of data through this new resource.
- Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease Consortium, a team-science venture to build a nuanced model of Alzheimer's disease that more accurately reflects its many causes and pathways. Scientists from diverse fields using the latest methodologies will work collaboratively towards shared goals: to dissect the complex molecular mechanisms by which vascular risk factors influence Alzheimer's disease and identify new targets for treatment and prevention.
- MIND Diet Intervention to Prevent Alzheimer Disease: NIA has recently funded this Phase III randomized controlled trial designed to test the effects of a 3-year intervention of a hybrid of the Mediterranean and DASH diets, called MIND, on cognitive decline among 600 individuals 65+ years without cognitive impairment who are overweight and have suboptimal diets that may place them at risk for developing dementia.
- Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study, led by researchers at the Memory Impairment and Neurodegenerative Dementia (MIND) Center at the University of Mississippi Medical Center. Researchers are studying, in a biracial population, age-related cognitive decline and the transition from mild cognitive impairment to dementia, with an emphasis on potentially modifiable vascular risk factors. Funding for this important study was renewed in 2015.

QUESTIONS SUBMITTED BY SENATOR SHELLY MOORE CAPITO

MEDICATION-ASSISTED TREATMENT

Question. Ensuring access to treatment for opioid addiction is essential to reversing the number of overdose deaths and the overall opioid epidemic. Medication-Assisted Treatment (MAT) plays an important role in this treatment. Current treatments such as methadone and buprenorphine—while effective in many cases—often require continued use for long periods of time, sometimes years, and daily maintenance. Is NIDA researching new methods of MATs which would address these issues?

Answer. MAT, which includes the use of methadone, buprenorphine, or naltrexone in combination with behavioral therapy and appropriate wrap-around services, is highly effective for the treatment of opioid use disorders (OUDs). Like other chronic illnesses (diabetes, cardiovascular disease), effective treatment for OUD currently requires ongoing treatment. Abundant scientific data show that long-term use of maintenance medications successfully reduce illicit drug use, reduce the risk of relapse and overdose, reduce associated criminal behavior, and help patients return to a healthy, functional life.¹⁵

MAT is the current standard of care for OUD; however, there is a longstanding misconception that methadone and buprenorphine, which control opioid craving and withdrawal, merely “substitute one addiction for another”. This belief has reinforced scientifically unsound “abstinence-only” philosophies in many treatment centers and limited the use of these medications. In reality, when properly prescribed, these medications do not get the patient “high”, they restore balance to brain circuits that are impaired by addiction and allow the patient to return to more normal levels of functioning. However, these medications require regular dosing and frequent—sometimes daily—healthcare appointments that can be burdensome for many patients. NIDA research is exploring ways to improve the treatment of OUDs including:

Development of non-opioid based medications and treatments:

- Lofexidine is an alpha2A-adrenergic receptor agonist that is currently being evaluated as an adjunct treatment for cravings and withdrawal to reduce the doses of buprenorphine or methadone needed to treat OUD. NIDA, through a

¹⁵The American Society of Addiction Medicine (2013). Advancing Access to Addiction Medications.

public-private partnership with US WorldMeds LLC, supported a Phase III Clinical Trial examining the safety and efficacy of Lofexidine in buprenorphine-maintained patients at 13 sites. If approved, Lofexidine will be the first non-narcotic medication approved by the FDA to treat opioid withdrawal.

—NIDA is supporting research examining multiple new targets to treat OUD, including Doxazosin (alpha1 adrenergic receptor blocker); Zonisamide (sulfonamide anticonvulsant); Lorcaserin (5HT2C serotonin agonist); and NT-814 (neurokinin receptor antagonist).

—Anti-opioid vaccines—NIDA is currently supporting the development of several vaccines that bind to opioids within the body and prevent them from entering the brain. Vaccines currently in development can bind to heroin or prescription opioids or both, while another targets both opioids and HIV to simultaneously protect against HIV infection while reducing the rewarding effects of opioids.

Improving current medications and treatment regimens:

—*Probuphine Buprenorphine Implant*.—Probuphine provides a new treatment option for people in recovery who may value the unique benefits of a six-month implant compared to other forms of buprenorphine, such as the possibility of improved patient convenience from not needing to take medication on a daily basis. A New Drug Application (NDA) that includes results from a Phase III double-blind clinical study was resubmitted in September of 2015. FDA action is expected this year.

—*Re-Engineering Methadone Treatment*.—Ongoing research is testing strategies to redesign methadone treatment programs to offer more patient-centered care that improves the counselor-client relationship, treatment retention, patient outcome, and cost-efficiency.

—*Comparative Effectiveness of MATs*.—Methadone, buprenorphine, and naltrexone are all effective for treating OUD. NIDA is funding comparative effectiveness studies to determine which medications work best for specific populations including opioid-dependent youth and HIV-positive patients.

—*Biomarkers for Pain*.—NIDA supports imaging studies of pain-altered brain function as well as molecular markers in order to identify biomarkers for pain conditions.

—*Partnerships to Improve Service Delivery*.—In response to the high rates of opioid overdose in Appalachia, NIDA has partnered with the Appalachian Regional Commission to fund research to address injection opioid use and its consequences in the Appalachian Region to determine how best to leverage available resources and programs to address the epidemic, and to improve service delivery.

—*Implementation Science for Improved Medication Assisted Treatment (MAT) Delivery*.—Several NIDA-supported investigators are developing and testing strategies to facilitate the effective and sustainable implementation of MAT in settings with high rates of opioid use disorders including criminal justice settings, emergency departments, and HIV treatment settings.

—*Mobile Health and Telehealth for Improved Delivery of MAT*.—NIDA also funds the development and testing of technology-based tools to facilitate communication between patients and providers; improve patient adherence; help providers deliver more patient-centered care for OUD; and improve client motivation and build their skills to achieve better outcomes.

QUESTIONS SUBMITTED BY SENATOR JEANNE SHAHEEN

INSTITUTIONAL DEVELOPMENT AWARD PROGRAM

Question. Dr. Collins, I was very pleased Congress provided a significant increase in funding for NIH in last year's budget. So many people who are affected by disease look to the NIH for hope that one day a cure can be found that will help them live longer and healthier lives. Thank you for your leadership.

I was also very pleased that the NIH Institutional Development Award program received a significant increase in the fiscal year 2016 omnibus. As you know, New Hampshire is a very active participant in the program and it has helped us build new research infrastructure and recruit the new generations of research scientists our Nation needs for the future. I think New Hampshire has important contributions that we can make to support NIH's biomedical research mission.

The president's request has an over budget increase for fiscal year 2017. Do you think the budget for the Institutional Development Award program should grow along with the budget for NIH?

Answer. Funding for the IDeA program was held flat relative to fiscal year 2016 in the President's fiscal year 2017 Budget Request, consistent with the overall proposed fiscal year 2017 NIGMS budget and the proposed budget for other NIH Institutes and Centers excluding special targeted Presidential initiatives.

QUESTIONS SUBMITTED BY SENATOR BRIAN SCHATZ

OPIOIDS

Question. When discussing the urgent need to address the public health crises of chronic pain and opioid abuse, you stated that “we need new alternatives for pain management and the NIH and our partners will develop them.” Despite the substantial human and economic burden of chronic pain on our Nation, according to the NIH Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC), the NIH only spent \$463 million on pain research in fiscal year 2015, with a near-flat estimate of \$481 million for fiscal year 2016 and fiscal year 2017 (equal to an investment of less than five cents per person with chronic pain). Please outline the NIH's specific plan for fiscal year 2017 to increase the NIH's investment in pain research and to develop and implement a targeted basic, translational, and clinical research effort that will: elucidate the underlying biological mechanisms of chronic pain; develop and discover safe, effective pharmacologic and non-pharmacologic therapies that can replace the use of addictive medications in the treatment of chronic pain; and populate an evidence base that can inform clinical strategies and care. With which Federal agencies will the NIH partner? Which person, institute(s), center(s), or office(s) within the NIH will be responsible for overseeing and implementing this effort across the NIH and in conjunction with other agencies? Which NIH initiatives hold the most promise for achieving these goals in a time- and cost-effective manner (e.g., Advanced Medicines Partnership, public-private partnerships through NCATS, Precision Medicine Initiative, BRAIN Initiative)? What is the associated timeline and budget for this effort?

Answer. The societal and individual benefits derived from improved pain management are significant, and a continued investment in NIH is needed to advance research to discover new and effective therapies. NIH is committed to advancing pain research with the ultimate goal of reducing the burden of pain and improving safe and effective pain care. Several principles govern how NIH sets its research priorities: scientific merit, scientific opportunities, public health needs, and portfolio balance. NIH funds a broad range of pain research spanning basic, translational and clinical studies. Through efforts of the NIH Pain Consortium, funding for pain research has nearly doubled since 2003. In light of the heightened awareness of the opioid and chronic pain crises and the release of the HHS National Pain Strategy (NPS), NIH has responded to the need to enhance the pain research agenda and is acting through several strategies.

NIH, along with Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), Food and Drug Administration (FDA) and Veterans Administration (VA) currently is engaged in developing a long-term Federal Pain Research Strategy (FPRS). The effort is coordinated by NIH and the Interagency Pain Research Coordinating Committee (IPRCC). NIH's Office of Pain Policy under the direction of Dr. Linda Porter, National Institute of Neurological Disorders and Stroke (NINDS), is implementing the effort. The objectives of the strategy are to review the current state of federally supported pain research, identify gaps and research needs and prioritize recommendations to advance the Federal research agenda. A panel of experts will provide recommendations on basic, translational, and clinical research as it relates to the continuum of pain from prevention through chronic pain management. The full spectrum of research will be addressed, from biological mechanisms through development of novel safe and effective therapies. The timeline for completion of the strategy is January, 2017.

Pain research is supported by nearly all Institutes across NIH. The NIH Pain Consortium is a trans-NIH entity that includes members from 25 Institutes and Centers (ICs) and is chaired by Dr. Koroshetz, Director NINDS. It was established to coordinate pain research efforts across NIH. It supports many shared funding opportunities that span the interests of multiple ICs and in some cases those of other Federal agencies. See: http://painconsortium.nih.gov/Funding_Opps/highlighted-initiatives.html.

The BRAIN initiative provides opportunities to elucidate the neuronal pain circuitry and dysregulation of neuronal processing associated with chronic pain and as such is highly relevant to the pain research agenda. In addition the Precision Medi-

cine Initiative is creating a large dataset from a cohort of more than a million Americans that will include information about pain symptoms, analgesic use, patient characteristics, clinical outcomes, and self-reported outcomes—providing a resource with tremendous promise for advancing pain research.

The reliance on opioids for chronic pain management and its associated harms has heightened the need to develop and promote novel approaches to integrated pain care that are safe, effective, and not reliant on opioids. NIH currently funds research that includes development of non-opioid and non-addictive opioid analgesics, trials for effectiveness of integrated pain care, development of novel non-pharmacological treatment approaches, and exploration of new drug targets. NIH hosted the Pathways to Prevention Workshop on long-term use of opioids for chronic pain. Follow-up meetings with Federal partners, focused on research priorities from the workshop and ways that Federal agencies can coordinate efforts to address the priorities, including the development of non-opioid pain therapies and multidisciplinary approaches to care.

One challenge faced by NIH is the small size of the pain research community, which limits the number of applications and in turn, the level of NIH funding for pain research. NIH continues its concerted effort to expand the field by encouraging junior and non-pain investigators to enter into pain research through funding incentives that promote early career stage pain researchers, and specifically call for multidisciplinary pain and non-pain investigators to collaborate (e.g., http://painconsortium.nih.gov/Funding_Opps/highlighted-initiatives.html). NIH also regularly provides training workshops at scientific meetings of pain specialists. Expansion of the research community is a crucial step toward increasing funding levels for pain research to ensure that these dollars are directed to high-quality, innovative research.

NIH hopes that the efforts described here will contribute to a Department of Health and Human Service (HHS)-wide effort to expand research needed to address the ongoing opioid crisis and the broad priorities identified in NPS and in the ongoing FPRS. It is NIH's hope that once fiscal year 2017 is completed, the full set of pain-related research applications awarded will lead to a higher amount of funding than the current fiscal year 2017 estimate indicates.

NIH appreciates the significance of the public health and economic burden of pain and will continue to develop partnerships across our institutes and other Federal agencies to enhance and improve our pain research agenda.

TELEHEALTH

Question. We've spoken before about telehealth and remote patient monitoring, and how these technologies can improve outcomes and save money. I know that the NIH has supported a lot of work on mobile health, or mHealth. Can you please give me an update on the research currently being funded at NIH on telehealth?

Answer. Telehealth approaches leverage communications technologies to provide and support healthcare at a distance. NIH is committed to the development of telehealth approaches that enable people to take advantage of medical advances, regardless of their circumstances. Many NIH-sponsored research projects are funded as parts of initiatives supporting small business innovations. These small businesses are translating scientific and technological advancements into tools for the practice of medicine in a diverse range of settings. Other projects are the result of investigator-initiated exploratory applications that push the boundaries of how we approach medical treatment and care.

NIH has a history of targeted efforts to stimulate growth in the telehealth space. As early as 1994, the National Library of Medicine's High Performance Computing and Communications awards sought out applicants developing telemedicine and telehealth approaches.¹⁶ The National Institute of Biomedical Imaging and Bioengineering (NIBIB) has also championed the advancement of telemedicine with targeted programs and general support.¹⁷ These founder programs established NIH-wide support of telehealth development. Their impact is evidenced in the major themes of NIH-funded telehealth research:

—*Overcoming Barriers.*—Today, there are many barriers for some patients, including physical and logistical constraints, to receiving adequate care and treatment in the traditional medical setting. Telehealth research funded by the NIH aims to bring the clinic to the patient, and the specialist provider to the gener-

¹⁶ Advanced Technology Focus of 12 HPCC Health Care Awards. (1997, April 3). Retrieved April 21, 2016, from <https://www.nlm.nih.gov/archive/20041229/research/telemedhpcc.html>.

¹⁷ Telehealth. (2013, January 22). Retrieved April 21, 2016, from <https://www.nibib.nih.gov/science-education/science-topics/telehealth#1431>.

alist, with tools that allow for healthcare-related exchanges remotely. For example, investigators on a recently funded project at the University of Texas, Austin, are piloting teleconsultation methods that allow low-income, house-bound seniors to receive mental health counseling.¹⁸ Other NIH-funded researchers are investigating the use of extant social infrastructure, such as community churches, as hubs for the receipt and distribution of medical care and information related to obesity and type 2 diabetes.¹⁹ In addition, researchers at the University of Washington are harnessing the reach of telehealth approaches to help manage coordinated care efforts for women with perinatal depression.²⁰

—*Remote Access to Care.*—While the last decade has brought major technological and intellectual advances to the field of medicine, these advances are not always readily available at the myriad points of care upon which people are dependent. Another focus of NIH-funded telehealth research is building diagnostic tools that free patients and providers from the constraints of the hospital or clinic. Along these lines, a group at Massachusetts General Hospital is pioneering technology to enable smartphones to be used as confocal microscopes to help diagnose AIDS-related Kaposi sarcoma, while scientists at Emory University are leveraging mobile technologies to create automated web-based methods for early, remote diagnosis of Alzheimer's disease.^{21,22} NIH funding is also enabling the development of remote diagnostics for conditions like traumatic brain injury, HIV, Ebola and other infectious diseases, and breast cancer.^{23,24,25,26,27,28}

—*Remote Patient Monitoring.*—Diagnosis is a first step, but chronic conditions regularly need frequent monitoring by healthcare providers. Moreover, it is often critical that emergent, life threatening events are identified as soon as possible to enable effective interventions. NIH is funding research that enables this remote patient monitoring, like efforts by biotechnology companies to develop a disposable assay to monitor heart failure at home in at-risk patients and imbedded biosensors to monitor patients' blood levels of chemotherapy agents in real time.^{29,30}

NIH recognizes the promise of telehealth approaches that allow for delivery of quality healthcare in a range of settings. Not only has NIH funded discrete research projects that advance the field of telehealth, the agency has woven telehealth applications development and evaluation into the fabric of large, trans-NIH and intergovernmental initiatives like the Precision Medicine

Initiative. As one of its founding principles, NIH is committed to improving the health and wellbeing of all people, regardless of their circumstances. As such, NIH will continue to fund cutting edge research, such as telehealth development, that helps to realize these principles.

RESEARCH CENTERS IN MINORITY INSTITUTIONS PROGRAM

Question. The legislation that established the Research Centers in Minority Institutions (RCMI) program in 1985 was intended to “strengthen the research environment” of “predominantly minority institutions” that “offer degrees in the sciences related to health but which heretofore have not received significant amounts of research support.” NIH moved to accomplish this goal by, as stated in the most recent Funding Opportunity Announcement (FOA), providing funds to “(1) develop and enhance the institutional research infrastructure necessary for the conduct of biomedical and/or behavioral research; (2) enable minority institutions to become more successful in obtaining competitive extramural support for the conduct of biomedical and/or behavioral research; and (3) enhance the biomedical research environment at these institutions.” The RCMI program has benefited numerous minority institutions, including through the growth of NIH funding, increased publications and presentations, the recruitment and retention of excellent faculty, and much more.

¹⁸ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8927954.

¹⁹ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8994598.

²⁰ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9008381.

²¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9018555.

²² https://projectreporter.nih.gov/project_info_description.cfm?aid=8704932.

²³ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8969564.

²⁴ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8905469.

²⁵ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9141791.

²⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9115796&icde=30006803&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC.

²⁷ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8891696.

²⁸ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9133217.

²⁹ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8905933.

³⁰ https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8839582.

I support the intent of the RCMi program as originally enacted. However, we have been hearing that NIH may be considering changes to this program. Can you please address the following:

- Will non-minority institutions become eligible for RCMi funding?
- Will institutions that have received “significant amounts of Federal funding” now be allowed to compete?
- Will awardee institutions no longer be allowed to fund pilot projects within the institution to increase the competitiveness of their faculty?
- Will it be necessary to distribute RCMi funding across a variety of disciplines in the awardee institution, i.e., basic biomedical science, socio-behavioral science, and clinical population studies, rather than focusing on their institutional strengths in order to increase competitiveness?

Answer. Eligibility of the RCMi program has historically been tied to doctoral degree granting institutions of higher education designated as a “minority institution” by the Department of Education. The National Institute on Minority Health and Health Disparities (NIMHD) is committed to keep the intent of the RCMi program and will continue to engage institutions that are less research intensive based on overall NIH funding and have a history of supporting students and trainees under-represented in biomedical research and to serving diverse populations.

Consistent with the intent of the RCMi program, the priority continues to be strengthening the research environment at the institution. There are multiple ways to accomplish that goal, from providing specialized expertise such as biostatistics, health informatics or specific research skills in laboratory science, to conducting specific research projects in minority health or health disparities. Moreover, NIH recognizes the value of small scale pilot projects to enhance the expertise and career of junior faculty and agrees that it is a valuable component of the RCMi program.

Individual RCMi institutions have and will continue to be able to focus on different scientific areas including basic biomedical, behavioral, and/or clinical research that best align with the strengths of their institution.

Since the transfer of the RCMi program to NIMHD in 2012 with the dissolution of the National Center for Research Resources (NCRR), NIMHD has made it a priority to integrate the RCMi program into the existing NIMHD portfolio. NIMHD has focused on specific programmatic goals and objectives in order to minimize overlap and maximize the scientific benefit of the Federal resources and plans to provide updated guidance to the extramural research community in the summer of 2016.

QUESTIONS SUBMITTED BY SENATOR TAMMY BALDWIN

ETHICAL ISSUES SURROUNDING NON-HUMAN PRIMATES

Question. Dr. Collins, I understand that NIH has plans to develop a summer workshop on ethical issues surrounding research with non-human primates. Can you please share additional background on this workshop?

Which Institutes or Centers are organizing the workshop, and who will be responsible for choosing the participants?

Is NIH employing a broad range of experts on research with these animals in order to ensure an open dialog that reflects the significant scientific investments NIH has in this type of research?

Answer. Research with animals, including non-human primates, continues to revolutionize our understanding of human health and disease, and has enabled the development of treatments and cures for a wide array of devastating diseases and conditions. Non-human primates are a particularly valuable resource for answering the most complex questions facing human health, as these animals share similar anatomy, physiology, and behavior with humans. For instance, scientific and treatment advances for Parkinson’s disease have been a direct result of research with non-human primates, both in the development of a disease model and the innovative clinical application of research technologies such as deep brain stimulation. Also, in response to the 2014–2015 outbreak of Ebola in West Africa, research using non-human primates was critical in the development of potential new experimental vaccines now being evaluated in clinical trials.

That being said, the decision to use non-human primates in a particular study is not taken lightly. Research must satisfy ethical principles of scientific rigor, appropriateness of the model, and consideration of animal welfare. Upholding these precepts remains a steadfast commitment of biomedical research and has been estab-

lished in policy since the passage of the Animal Welfare Act in the mid-1960s.³¹ All NIH-funded research with animals is reviewed to ensure that the science is highly meritorious and the welfare of the animals is appropriately protected. NIH has established numerous policies, procedures, and protocols to ensure all appropriate principles are followed, including taking animal welfare concerns very seriously. The Office of Laboratory Animal Welfare ensures this oversight framework is followed. Its mission is to address humane care and use of animals in HHS-supported research, testing, and training by guiding researchers and interpreting the Public Health Service Policy on Humane Care and Use of Laboratory Animals.³²

NIH remains confident that the oversight framework for the use of non-human primates in research is robust and has provided sufficient protections to date. However, the Agency acknowledges that a periodic review of its policies and processes ensures that this framework evolves in a manner consistent with emerging scientific opportunities and public health needs.

Toward this end, NIH plans to convene experts in science, policy, ethics, and animal welfare to discuss the oversight framework governing the use of non-human primates in NIH-funded biomedical and behavioral research endeavors. At this workshop, NIH will explore the current state of science of NIH-supported research involving non-human primates as research models and discuss how existing regulations and policies address their continued responsible use in research.

The NIH Office of Science Policy, which is part of the NIH Office of the Director, is organizing this workshop, which will occur later this fiscal year. During the planning process, the NIH Office of Science Policy will consult with NIH Institutes and Centers that fund research using non-human primates, the Office of Laboratory Animal Welfare, and the Department of Bioethics to identify a diverse and knowledgeable group of speakers and panelists for the workshop. The workshop participants, both internal and external to NIH, will represent the Agency's significant scientific investment in research utilizing non-human primates and provide a thorough and productive dialogue to support the continuation of ethical and responsible research using nonhuman primates.

SUBCOMMITTEE RECESS

Senator BLUNT. And the subcommittee stands in recess.

[Whereupon, at 12:00 p.m., Thursday, April 7, the subcommittee was recessed, to reconvene subject to the call of the Chair.]

³¹<https://awic.nal.usda.gov/government-and-professional-resources/Federal-laws/animal-welfare-act>.

³²<https://grants.nih.gov/grants/olaw/references/phspol.htm>.

MATERIAL SUBMITTED SUBSEQUENT TO THE HEARING

[CLERK'S NOTE.—The following outside witness testimonies were received subsequent to the hearing for inclusion in the record.]

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 2017 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.

INNER EAR BLUEPRINT MAY LEAD TO TREATMENT FOR HEARING LOSS AND BALANCE DISORDERS

Approximately 50 percent of Americans ages 75 and older have a disabling hearing loss. In addition, more than 1 in 20 children in the United States between the ages of 3 and 17 have a dizziness or balance problem. To determine the causes of hearing loss and balance disorders, it is important to understand how the cells in the inner ear form. To do this, scientists are identifying gene expression maps of the inner ear cells. Understanding inner ear cell development could lead to ways to regenerate lost or damaged cells and restore hearing and balance.

Specialized sensory epithelial cells in the inner ear are responsible for hearing and balance. These cells, which include hair cells and supporting cells, are located in the cochlea, the snail-shaped structure in the inner ear, and work together to detect sound. Similar types of hair cells and supporting cells are also found in the utricle, a fluid-filled pouch located near the cochlea, which plays a critical role in helping us maintain our balance. These cells detect how we move our heads, how our heads are positioned and whether we are moving or stationary; this information tells our brain, for example, whether we are standing or lying down. The utricle is one of several structures and organs in the body that provide our sense of balance.

Hair cells and supporting cells can be damaged by medications, infections or disease, injury, exposure to loud noises, or aging, leading to hearing loss and balance problems. In humans, these cells cannot naturally repair themselves, so effective treatments are limited. In addition, there are only a few thousand of these sensory cells and they are located in a bony channel embedded in the skull, making them difficult to study.

Using a sensitive new technology called single-cell RNA-seq, NIDCD intramural scientists have created the first high-resolution gene expression map of a single cell within the newborn mouse inner ear. By analyzing the cell's gene activity profiles, the scientists were able to identify genes that are active at different stages of development. The findings provide new insights into how epithelial cells in the inner ear develop and differentiate into the specialized cells that serve critical functions for hearing and maintaining balance. Understanding how these important cells form may provide a foundation for the potential development of cell-based therapies for treating hearing loss and balance disorders.

MINI INNER-EAR DRUG DELIVERY DEVICE COULD HELP COMMON HEARING AND BALANCE PROBLEMS

Approximately 37.5 million American adults report some degree of hearing loss and almost eight million adults report a chronic problem with balance. Common examples include middle-ear infections (otitis media), Ménière's disease, noise-induced hearing loss, tinnitus, age-related hearing loss, dizziness, and vertigo. Hearing and balance disorders also decrease quality of life, and they cross all ethnic and socioeconomic lines.

Developing drug treatments is a long and costly process. One of the first hurdles is developing drugs that are safe and effective. For drug therapies to treat hearing loss and balance disorders, a second hurdle is getting the drugs where they need to go, which is deep inside the skull to the inner ear. Developing a safe and efficient route to the inner ear represents a significant technical challenge. Another challenge is to determine the appropriate concentration or dosage of a drug to be delivered into the ear.

NIDCD-supported scientists are tackling these hurdles. Using microfluidic and microelectromechanical systems technologies, researchers developed a wearable miniaturized pump system that safely and effectively delivers drugs in various dosages over time to the inner ear in animal studies. The device can also take samples of the inner ear fluid, which will aid scientists in drug development and treatment.

The investigators hope to use this device in preclinical animal studies. They plan to make the micro-pump and its electronic components so small that someday the entire system can be implanted in an individual's mastoid cavity, an opening in the bone behind the ear. The device would enable programmable, automated, and long-term delivery of therapeutic compounds to the inner ear. Because it can target inner ear fluid precisely, the device will serve as a useful tool for investigating the molecular mechanisms associated with inner ear diseases and testing new drug treatments for hearing and balance problems.

Problems with Ability to Taste or Smell are Common in Middle-Aged and Older Adults People who have a poor ability to taste or smell can miss important cues to help them avoid dangers such as gas leaks, fire, and spoiled food. Scientists in the NIDCD Epidemiology and Statistics Program collaborated with the Centers for Disease Control and Prevention to conduct the first nationally representative survey about perceived taste and smell problems in more than 3,600 adults aged 40 and older. About 19 percent of U.S. adults ages 40 and older report having had a problem with their ability to taste, and approximately 23 percent report having had a problem with their ability to smell. The likelihood that a person will report a diminished sense of taste and/or smell increases with age. In adults ages 80 or older, nearly 31 percent report having had a problem with their sense of smell, and more than 27 percent have had a problem with their sense of taste. This survey was part of the Healthy People 2020 national objectives for improving the health of all Americans. The data help us gauge the scope of the problem. Future data releases will also include results of taste and smell tests and will give us our first look at prevalence of taste and smell problems in the United States.

SCIENTISTS GROW VOCAL FOLD TISSUE IN THE LAB

Vocal fold tissue is a complex biological structure that is responsible for normal voice production. About 7.5 million people in the United States have trouble using their voices. Voice problems can cause significant personal and occupational difficulties, loss of income, and reduced quality of life. People who have sustained injuries to the larynx or have undergone head and neck surgery can exhibit voice disorders. These disorders can range in severity from mild to total voice loss if the surgery was extensive for removal of a malignancy. NIDCD-supported voice scientists in collaboration with other NIH-supported researchers have bioengineered vocal fold tissue in the lab using human cells. Moreover, the tissue had physical qualities that allowed it to "behave" like normal vocal fold tissue. To see if it could transmit sound, the researchers transplanted the tissue into an animal model. The bioengineered tissue performed well and was not rejected by the recipient, which is usually a major obstacle in these types of surgeries. This proof-of-principle study provides hope that one day individuals who have lost the use of their voice because of loss of their laryngeal tissue will have better treatment options.

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 2017 budget request for the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH).

UNDERSTANDING OUR EXPOSURES

An oil rig explodes in the Gulf of Mexico impacting an entire region's way of life. A manufacturing plant spills thousands of gallons of toxic chemicals into a river in West Virginia creating unknown risks to nearby residents. A combination of aging pipes and corrosive water leaches lead into drinking water in Flint, Michigan, pos-

ing irreversible harm to the city's children. These recent events bring into stark relief the critical need for strong exposure science—the first step in responding to an environmental health emergency is to understand the nature of the threat. But as prominent, tragic, and increasingly common as such occurrences are, they represent only a small part of the thousands of potentially harmful chemicals, metals, and other environmental pollutants our Nation's people are faced with on a daily basis.

Protecting people's health from the consequences of such encounters requires knowledge, not only of the nature of the hazard itself, but just as importantly, of the means, amount, and effects of exposure to it. And further complicating our ability to determine our risk is the combination of human response variability and disparate exposures to environmental health threats. But such knowledge must be obtained if we are not only to respond to exposures after they occur, but be successful in the larger goal of avoiding harmful exposures, and thereby preventing illness and disease from ever occurring. The recognition of this fundamental scientific need is the basis of the work of NIEHS and the reason why our Institute has prioritized exposure science in its Strategic Plan. Although the issue of exposures is integrated throughout the plan, specific goals call for NIEHS to "Transform exposure science by enabling consideration of the totality of human exposures and links to biological pathways, and create a blueprint for incorporating exposure science into human health studies," and to "Understand how combined environmental exposures affect disease pathogenesis." I will describe just some of the ways in which NIEHS has made significant progress toward these goals and toward ensuring the health of the American people.

CONNECTING EXPOSURES TO OUTCOMES

Five years after the Deepwater Horizon (DWH) oil rig explosion, which caused the largest oil spill in U.S. history, NIEHS-supported researchers continue work in three related areas—a health effects study of oil spill cleanup workers called the GuLF Study, research partnerships between Gulf-area universities and community organizations, and an NIH disaster research response effort. The research team developed a job-exposure matrix that enabled scientists to characterize exposures of workers participating in the GuLF Study and assess possible links between reported health symptoms and the chemicals each worker was exposed to, and preliminary results are being analyzed. University-community partnerships are focusing on health concerns identified by communities after the oil spill, including pregnancy and birth outcomes, general physical and mental health of coastal residents, and seafood safety. A study of 2,126 adult women residing in Southern Louisiana enrolled in the Women and Their Children's Health (WaTCH) study showed that both physical/environmental and economic exposure to the oil spill was associated with an increase in self-reported physical health outcomes. On a positive note, a risk assessment of exposure to polycyclic aromatic hydrocarbons of Vietnamese-Americans, a large shrimp-consuming population in the area, showed no acute health risks or excess cancers, reducing concerns about shrimp consumption following the DWH spill.

Following the spill of 10,000 gallons of the chemical 4-Methylcyclohexanemethanol (MCHM) into the Elk River upstream of the municipal water intake of Charleston, West Virginia, NIEHS researchers were able to help allay the fears of the community and State officials through a timely assessment that combined exposure data with a suite of health effect prediction studies, including computer modeling and laboratory toxicity studies. Findings of these investigators provided additional support for the adequacy of the drinking water advisory set by the Centers for Disease Control and Prevention at the time of the spill as being protective of health.

In response to the latest public health disaster, the exposure of the population of Flint, Michigan, to lead in contaminated drinking water, NIEHS staff and grantees are leading efforts to understand residents'—especially children's—lead exposures to inform the public health response, both immediately and over the long-term. A long and continuing history of support of research on lead enables such efforts. Recent research by NIEHS grantees in Michigan demonstrated, for the first time, that lead exposure of pregnant mothers can affect DNA methylation patterns in their grandchildren, suggesting that a much longer-term perspective may be needed when considering measures to protect environmental health in the future. Also, NIEHS-funded research of lead-poisoned children in China recently established that measurement of lead in bone (through X-ray fluorescence) is a useful biomarker of lead exposure in children. Such research illustrates the kind of knowledge that might be applied to situations like the one in Flint. It is this kind of useful knowledge that NIEHS hopes to enable researchers to obtain through its recently established Children's Health and Exposure Assessment Resource (CHEAR), which will provide a

laboratory network, data repository, and an analysis center to leverage the public investments of NIH-funded scientists to better understand environmental exposures and human health.

Public health disasters such as chemical releases, hurricanes, infectious disease outbreaks, and others comprise unique exposure scenarios that can offer insights into environmental exposures encountered, not only by the affected communities and responders, but also by a broader range of the population. NIEHS, in collaboration with the National Library of Medicine, has developed the Disaster Research Response (DR2) program to further our national ability to gather time-critical exposure and health information to reduce adverse health effects and improve response, recovery, and preparedness for future events. At the same time, this program will facilitate discovery research and generate novel hypotheses that will add to the body of knowledge underlying exposure related conditions such as cancer, neurological, and immune diseases and disorders.

Disasters are compelling for both public and research attention, and deservedly so. But NIEHS efforts to elucidate the broad range of environmental exposures are far more proactive than responsive, and consistently generate findings that increase our ability to protect and improve people's health. For example, an ongoing project is using a matrix biomarker of tooth development to reconstruct the exposome—the compilation of multiple chemical exposures—over different life stages. A better understanding of how and when specific exposures occur will improve our ability to target interventions, particularly during critical windows of development. NIEHS-funded investigators also are working at the cutting edge of research on the microbiome, investigating interactions between the gut microbiome and exposure to arsenic, a known human carcinogen, and uncovering the relationship between obesity and exposure to ozone.

TRANSLATING SCIENCE INTO ACTION

NIEHS efforts are directly supportive of major health initiatives in the United States including Big Data to Knowledge (BD2K), the National Cancer Moonshot, and the Precision Medicine Initiative.

NIH's BD2K initiative is focused on developing new strategies to analyze and leverage the explosion of increasingly complex biomedical data sets. NIEHS is leading the program's Training and Workforce Development efforts. These awards support current and future generations of researchers to specialize in data science fields and in the use or generation of Big Data. A current awardee is working to establish new integrative and data-driven methods for building systems neuroscience models of executive functioning during childhood, reporting recent advances in improving the specificity of magnetic resonance imaging (MRI) scans.

The recently announced National Cancer Moonshot aims to bring about a decade's worth of advances in 5 years, in part by improving our ability to prevent cancer and detect it at an early stage. Cancer, like most other non-communicable diseases, is a result of a person's genetics, age, and environment (including lifestyle), and the World Health Organization estimates that nearly 20 percent of cancers may result from toxic chemical exposures. NIEHS-supported researchers continue to make groundbreaking advances in our understanding of the complex interactions between these three factors, leading to knowledge to inform cancer detection and prevention strategies, as well as treatments and therapies. For example, polycyclic aromatic hydrocarbons (PAHs) are probable carcinogens found in coal tar, diesel exhaust, and wildfire, cookstove, and cigarette smoke. People are primarily exposed to PAHs in mixtures, though current risk assessments focus on individual components. An NIEHS grantee and colleagues have developed a faster, more accurate method to assess cancer risk from mixtures of PAHs by evaluating bioactivity after short-term exposure.

An example of NIEHS contributions to potential cancer therapy lies in treatment of ovarian cancer. The recurrence rate of ovarian cancer exceeds 75 percent, and the success of subsequent chemotherapy is limited because of the progressive development of drug resistance. New NIEHS findings suggest that a novel mechanism, combined activation of an early growth factor (EGR1) and microRNA (MIR152), may provide a useful therapeutic strategy to overcome resistance to the chemotherapy drug cisplatin, and improve outcomes in ovarian cancer.

NIEHS research spans the spectrum of scientific inquiry from basic mechanisms to exposure science to clinical research aimed toward intervention and treatment. Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. Advances by NIEHS scientists are poised to make great contributions to the promise of precision medicine. These contributions range from identifying fac-

tors including autoantibodies, clinical factors, and environmental exposures at illness onset associated with the disease course of juvenile myositis, a group of rare and life-threatening autoimmune diseases in children, to developing a method for isolating certain rare cells of metastatic breast cancers in blood and profiling their gene expression to provide real-time warnings of emerging chemotherapy resistance.

CONCLUSION

To conclude, NIEHS continues to be at the forefront of environmental health: identifying emerging health threats, developing and implementing new technologies to characterize and analyze our exposure to the world around us, and leading the generation of knowledge of how our environment interacts with our genetics to cause illness and disease. And consistent with our mission, we will continue to lead these efforts in support of the Nation's initiatives to improve and ensure the health of the American people.

PREPARED STATEMENT OF JOSEPHINE P. BRIGGS, M.D., 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 2017 budget request for the National Center for Complementary and Integrative Health (NCCIH) of the National Institutes of Health (NIH).

The NCCIH is the lead Federal agency for scientific research on the usefulness and safety of complementary and integrative health practices. Complementary health approaches include mind and body interventions, such as massage, acupuncture, yoga, and meditation, and natural products, such as dietary supplements and probiotics. To address the need for objective evidence as to the safety and efficacy of many of these approaches, NCCIH supports rigorous scientific investigation to better understand how these interventions work, for whom, and the optimal method of practice and delivery.

The 2012 National Health Interview Survey (NHIS), conducted by the Centers for Disease Control and Prevention (CDC) with support from NCCIH, showed that one-third of U.S. adults use complementary and integrative health approaches. Many of these individuals seek these approaches to improve their health and well-being or to manage symptoms of chronic diseases or the side effects of conventional medicine. Natural products (dietary supplements other than vitamins and minerals) are the most commonly used complementary health approach, followed by deep breathing exercises and yoga.

REDUCING PAIN AND IMPROVING SYMPTOM 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 United States (11.2 percent) experience daily pain. In addition, nearly 40 million adults (17.6 percent) experience severe levels of pain and are likely to have worse health status than the general public.¹

CDC has classified fatal overdoses involving opioid analgesics, medications used to treat pain, as an epidemic. To help address this crisis, we need improved strategies for pain management so that healthcare providers are less reliant on prescribing opioids. NCCIH supports research to better understand pain and to identify effective nonpharmacologic approaches to reduce the duration and intensity of pain. For example, our intramural research program studies the role of the brain in perceiving, modifying, and managing pain. Specifically, scientists are investigating the role of the brain in pain processing and how emotion, environment, and genetics affect its perception.

Recent results from NCCIH's extramural research program are advancing our understanding of the mechanisms of action of mind and body interventions and helping determine their effectiveness for treating pain. For example, previous research showed that mindfulness meditation helps relieve pain, but the mechanism through which meditation exerts this effect is not well understood. New study results, funded in part by NCCIH, demonstrate that mindfulness meditation may work on a different pain pathway in the brain than opioid pain relievers. Since opioid and non-opioid mechanisms of pain relief interact synergistically, the results suggest that

¹Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *Journal of Pain*. 2015;16(8):769–780.

combining mindfulness-based and other pain-relieving approaches that rely on opioid signaling may be particularly effective.

Furthermore, study results published in the *Journal of the American Medical Association* expand the evidence base for the effectiveness of mind and body interventions. In the first randomized clinical trial to rigorously evaluate mindfulness-based stress reduction (MBSR) for young and middle-aged adults with chronic low back pain, researchers compared MBSR with usual care (UC) and cognitive-behavioral therapy (CBT). They found that individuals with chronic low back pain who received training in MBSR and CBT, compared with UC, demonstrated greater improvements in functioning and reductions in chronic low back pain at 6 months and 1 year following treatment. The persistence of these beneficial effects suggests that MBSR and CBT may provide patients with skills for long-term management of pain.

NCCIH is also working with other NIH Institutes and Centers, the Department of Veterans Affairs (VA), and the Department of Defense (DOD) to test improved pain management strategies. Military personnel, veterans, and their families often struggle with pain management and its associated comorbidities including opioid misuse, abuse, and disorder. NCCIH plans to support a clinical trial coordinating center to launch a multi-year program to develop and test the efficacy and effectiveness of nonpharmacologic approaches to pain management and comorbidities for our military and veteran populations. Additionally, NCCIH is collaborating on the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative to accelerate the development and application of technologies to study the brain. NCCIH also is leveraging its resources through the NIH Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program to better understand the mechanisms of action and the development of "electroceuticals" for therapies in which nerves are stimulated to control organ function.

ADVANCING RESEARCH ON NATURAL PRODUCTS

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, according to the 2012 NHIS. The use of dietary supplements at times poses risks. For example, adverse events related to dietary supplements are estimated to contribute to 23,000 emergency department visits in the United States each year.² To better inform consumers and their healthcare providers, NCCIH supports research on the biological mechanisms of the benefits and potential harmful effects of natural products, such as their interaction with medications and liver toxicity. In fiscal year 2015, NCCIH established a Center of Excellence for Natural Product-Drug Interaction Research. The Center is systematically examining methods for studying natural product-drug interactions; developing standardized protocols to clarify which interactions have clinical impact; and disseminating its findings and resources broadly. In essence, the Center is developing a roadmap for the study of natural product-drug interactions with the ultimate goal of improving the body of knowledge available to healthcare providers, patients, and researchers.

To further enhance NCCIH's natural products portfolio, NCCIH partnered with NIH's Office of Dietary Supplements (ODS) to fund five research centers in fiscal year 2015. These research centers focus on the safety of natural products, how they work within the body, and the development of innovative research technologies. Specifically, the three Botanical Dietary Supplements Research Centers will advance the understanding of the mechanisms through which complex botanical dietary supplements may affect human health and resilience. The two new Centers for Advancing Natural Products Innovation and Technology aim to propel chemical and biological investigation of natural products. Each is tackling unique research challenges. One center is working to improve the speed, breadth, and precision of the characterization of natural products by developing innovative cell-based screening approaches to uncover bioactive molecules of interest and their corresponding biological targets. The other center is coordinating and disseminating research technologies aimed at mining bioanalytical knowledge of natural products.

Spurring innovation and developing new methodologies may lead to alternative sources of medically relevant compounds. For example, researchers, supported in part by NCCIH, created an innovative method to produce opioid drugs from sugar using genetically modified yeast. Using genes from a variety of plants, mammals, and microorganisms, they created yeast cells that can perform the entire process of manufacturing the opioids thebaine and hydrocodone using sugar as the starting material—a process that involves more than 20 separate steps. This innovation

²Geller, AI, et al. Emergency department visits for adverse events related to dietary supplements. *N Engl J Med*, 2015;373:1131–40.

opens the door to additional novel approaches to generating needed medically relevant compounds in diverse settings. The new technique illustrates the potential value of genetically engineered yeast as a platform for producing many complex chemicals and materials and may help lead to better drug development in the future. Given this advance is moving ahead of regulations and policy, open discussions and decisions for the use and application of this technology will be needed.

ASSESSING CARDIOVASCULAR BENEFIT OF CHELATION THERAPY IN PATIENTS WITH DIABETES

NCCIH is leading a trans-NIH effort (with NHLBI, NIDDK, NIEHS) and funding a planning phase to replicate the previous NIH-funded Trial to Assess Chelation Therapy (TACT) in older heart attack patients with diabetes. “TACT 2” will assess if an intravenous solution, which includes ethylenediaminetetraacetic acid (EDTA)—a chemical used to treat environmental exposure to heavy metal toxicity such as lead or cadmium, will reduce cardiovascular events in diabetics. Its use for treating heart disease was found beneficial in TACT, particularly for diabetic patients over 50 years of age who had a previous heart attack, but needs replication before becoming universally accepted. Additional research to identify the mechanisms by which chelation may affect heavy metal body burden and cardiovascular disease risk is also being planned.

INSPIRING PUBLIC TRUST THROUGH STEWARDSHIP

NCCIH works diligently to be an efficient steward of the resources entrusted to us. Currently, we are undertaking strategic planning activities focused on prioritizing our future research investments in complementary and integrative health. Additionally, we are ensuring that research workforce needs, especially those of clinician-scientists, are addressed. NCCIH's new strategic plan is expected to be released this summer.

Due to the self-care nature of these complementary health approaches, the translation and dissemination of unbiased, evidence-based information is of great importance to NCCIH. Therefore, helping consumers, healthcare providers, researchers, and policymakers be better informed about the safety and effectiveness of complementary interventions continues to be our primary communication goal. NCCIH makes research findings available to the public through multiple platforms, including video, social media, and mobile applications.

CONCLUSION

NCCIH continues to support research and leverage its strategic partnerships to build the scientific evidence needed by consumers, healthcare providers, and policymakers regarding the safety and efficacy of complementary health approaches. By catalyzing innovation, NCCIH is advancing research on natural products and mind and body interventions.

PREPARED STATEMENT OF BRUCE CUTHBERT, PH.D., ACTING DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

Mr. Chairman and Members of the Subcommittee: I am pleased to present the President's fiscal year 2017 budget request for the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH).

I am particularly excited to discuss the ways in which NIMH is working to accelerate scientific progress by supporting research that will improve our understanding of mental illnesses, fueling the transformation of care for the greatest public health impact.

PUBLIC HEALTH BURDEN OF MENTAL ILLNESS

NIMH is vigorously pursuing its mission to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. Mental illnesses account for 21.3 percent of all years lived with disability in the United States, and an estimated 9.8 million American adults suffer from serious mental illness (SMI) each year, according to the Substance Abuse and Mental Health Services Administration (SAMHSA). People with SMI (in which the ability to function in daily life is significantly impaired) die 8 to 10 years earlier than the general population. The Centers for Disease Control and Prevention report that over 42,773 Americans died from suicide in 2014, more than twice the mortality from homicide or AIDS. Mental illnesses rank as the third most

costly medical conditions in the United States, in terms of overall healthcare expenditures, behind heart conditions and traumatic injury.

IMPROVING PRECISION IN RESEARCH ON MENTAL ILLNESSES

Precision medicine means getting the right treatment at the right time to the right person. While significant advances in precision medicine have been made for select cancers, this is still not feasible for most other disorders, including mental illnesses. NIMH's approach to precision medicine revolves around the Research Domain Criteria (RDoC) initiative, which is intended to break mental illnesses down into fundamental mental processes (e.g., attention) compared across biological (e.g., genes, brain circuits) and behavioral (e.g., wakefulness) measurements.

Results from a recent NIMH-funded study lend support to the RDoC approach. The Bipolar Schizophrenia Network on Intermediate Phenotypes (BSNIP) study used "biomarkers"—or measureable indicators of disease—to sort patients with psychotic symptoms into "biotype" categories. The BSNIP study demonstrated that biotypes outperformed traditional diagnostic categories of psychotic disorders, such that sorting individuals with psychotic symptoms into subgroups based on brain biology can lead to greater precision in diagnosis, and potentially treatment. In fiscal year 2017, NIMH will continue to solicit research using RDoC approaches.

The success of RDoC relies heavily on a culture of open science and rapid data sharing, which NIMH has formalized by creating a set of data sharing repositories called the NIMH Data Archive (including databases for RDoC, autism research, and clinical trials). Through these types of initiatives, NIMH is maximizing the use and impact of a valuable asset: our shared data.

REVOLUTIONIZING OUR UNDERSTANDING OF MENTAL ILLNESSES

Together with other NIH Institutes and Centers, NIMH co-supports two large-scale neuroscience initiatives: The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and the Human Connectome Project (HCP). The BRAIN Initiative will accelerate the development and application of innovative technologies to identify how individual cells and complex neural circuits interact, filling major gaps in our knowledge about how the human brain functions. HCP is a collaborative neuroimaging effort to map the neural pathways underlying human brain function; the primary purpose is to acquire data on the structural and functional connectivity of the human brain and to facilitate rapid access to large HCP datasets for secondary data analyses by other researchers. HCP and the BRAIN Initiative will set the stage for future studies of abnormal brain circuits, thereby advancing our understanding of the origins of mental illnesses.

EARLY INTERVENTION CHANGES TRAJECTORY

NIMH recognizes the vital importance of early diagnosis and rapid delivery of appropriate and comprehensive treatment for mental illnesses. Approximately 100,000 adolescents and young adults experience a first episode of psychosis (FEP) each year in the United States, and the majority of people with SMI experience significant delays when seeking care.

To help reduce the duration of untreated psychosis, NIMH is collaborating with SAMHSA to translate findings from the NIMH Recovery After an Initial Schizophrenia Episode (RAISE) project into guidance for States regarding evidence-based approaches to early psychosis treatment. Utilizing coordinated specialty care (CSC), people experiencing FEP were connected with specialty care providers at the earliest stages of illness. RAISE investigators have shown that CSC is effective and can be implemented in community treatment settings nationwide. In fact, the Centers for Medicare & Medicaid Services recently extended Medicaid coverage of evidence-based interventions such as CSC for individuals experiencing FEP. This fast-paced expansion in reimbursement practices is rare, but is a promising example of how NIMH-funded research can be quickly translated into practice.

NIMH will build on the RAISE project with plans to launch the Early Psychosis Intervention Network (EPINET). EPINET uses a learning healthcare model to optimize care for youth at high risk to reduce the incidence of psychosis. With patients' consent, EPINET clinics will create a database of clinical information to help clinicians and researchers learn more about the effectiveness of early psychosis treatment.

In addition to early intervention for FEP, NIMH launched several major initiatives to intervene early to implement a prioritized research agenda for suicide prevention. The Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) study is poised to improve screening for youth at risk of suicidality following an emergency department admission; the Suicide Prevention for at Risk Indi-

viduals in Transition (SPIRIT) study, a collaboration with the U.S. Department of Justice, will evaluate the effectiveness of an evidence-based intervention among persons recently released from jail or prison; and the Reducing the Incidence of Suicide in Indigenous Groups—Strengths United through Networks (RISING SUN) initiative aims to create common outcome measures for suicide prevention efforts among indigenous peoples. These efforts represent NIMH's continued commitment to determining the best methods to prevent suicide, particularly among high risk populations.

In 2016 and beyond, NIMH will continue to strive toward achieving the ambitious goals of the NIMH Strategic Plan for Research by harnessing the potential of the BRAIN initiative, the RDoC and RAISE projects, and efforts to prevent suicide. These and many other research endeavors represent NIMH's ongoing commitment to achieving its vision of a world in which mental illnesses are prevented and cured.

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 2017 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 not only pursue a robust research portfolio in the areas of microbiology, infectious diseases, immunology, and immune-mediated disorders, but also to quickly launch a research response to newly emerging and re-emerging infectious diseases. This dual mandate has been particularly evident over the past 2 years as NIAID has accelerated research to address the unprecedented Ebola and Zika virus outbreaks.

INFECTIOUS DISEASES RESEARCH

NIAID continues to advance research to address emerging and re-emerging infectious diseases around the world. In recent years we have faced major threats from diseases that have caused substantial morbidity and mortality, with Ebola virus disease and Zika virus disease being perhaps the most notable; however, other diseases such as dengue and chikungunya also have raised significant concerns. NIAID research supports progress against these and other emerging and established infectious disease threats worldwide. Examples of notable NIAID-supported infectious diseases research are highlighted below.

Zika and other mosquito-borne viruses. The appearance and rapid spread of Zika virus in the Americas has coincided with new and concerning presentations of disease. These include reported increases in the birth defect microcephaly and the immune-mediated neurological disease Guillain-Barre syndrome. NIAID has rapidly mobilized research to address the public health threat of Zika by building upon our prior successes with other flaviviruses, notably West Nile and dengue viruses. Ongoing NIAID efforts include studies of the natural history, viral genetics, and pathogenesis of Zika virus, including how infection may cause the development of microcephaly and other congenital abnormalities in the fetus. In addition, NIAID is expanding efforts to develop countermeasures for Zika virus that could help control current and future outbreaks. NIAID has developed an animal model to test whether therapeutic compounds with activity against other flaviviruses also are effective against Zika virus. NIAID-supported researchers are developing diagnostics that can distinguish Zika virus from other flaviviruses, as well as investigating unique biosignatures that could form the basis of rapid, specific, and sensitive Zika diagnostic tests. The development of safe and effective vaccines against not only Zika but also several other mosquito-borne viruses is a top priority of NIAID. The NIAID Vaccine Research Center (VRC) is developing a DNA-based vaccine for Zika virus that is similar to a West Nile virus vaccine previously developed by NIAID. Phase I clinical testing of the West Nile vaccine candidate showed it was safe and generated a robust immune response, indicating it could be a promising platform for a Zika vaccine. NIAID scientists also are designing a live-attenuated Zika vaccine. This effort employs an approach similar to that used for an NIAID-developed dengue virus vaccine candidate currently in Phase III clinical trials in Brazil. In addition, NIAID is investigating a Zika virus vaccine candidate that uses the same platform as an Ebola vaccine tested in West Africa and is partnering with BARDA to support a whole-particle inactivated vaccine candidate. We anticipate that one or more of these Zika virus vaccine candidates will begin clinical testing in September 2016. NIAID also has supported the development of additional vaccine candidates

for mosquito-borne viruses, notably an NIAID VRC-developed chikungunya vaccine candidate currently undergoing Phase II clinical trials in the Caribbean.

Ebola. Longstanding NIAID investments in biodefense research and collaboration with industry partners enabled the rapid and successful execution of clinical trials of candidate Ebola countermeasures in response to the 2014–2016 Ebola outbreak in West Africa. Recently completed NIAID studies demonstrated that the experimental Ebola vaccines cAd3–EBOZ and rVSV–ZEBOV are safe and immunogenic. A clinical trial evaluating ZMapp, a cocktail of three Ebola virus antibodies, found that treatment with ZMapp likely benefits Ebola virus disease (EBVD) patients. ZMapp remains the leading Ebola therapeutic candidate and has been made available to the recent Ebola cases in Guinea. Finally, ongoing studies in Liberia are enhancing our understanding of the long-term health consequences in survivors of EBVD. NIAID researchers and colleagues recently described initial findings concerning the extent of eye, musculoskeletal, and neurological problems experienced by EBVD survivors, as well as a possible persistent risk of sexual transmission of the virus. These NIAID studies have validated the use of randomized, controlled clinical trials during an infectious disease outbreak. Our efforts continue to evaluate improved vaccine strategies to prevent Ebola virus infection and determine the long-term clinical and public health consequences of EBVD.

HIV/AIDS. Significant progress has been made in combating HIV/AIDS through the implementation of treatment and prevention approaches supported by NIAID research. Despite this progress, continued investment in the development of a safe and effective HIV vaccine and cure is needed to achieve a durable end to the HIV/AIDS pandemic. Research supported by NIAID continues to provide the evidence that informs the development of improved HIV treatment and prevention tools. A recent groundbreaking NIAID study conclusively demonstrated the value of early use of antiretroviral drugs, showing that starting treatment as soon as possible after HIV diagnosis reduces the risk of developing AIDS or other serious illnesses. Growing evidence from clinical trials and real-world implementation supports an approach known as pre-exposure prophylaxis, or use of antiretroviral drugs by high-risk HIV-negative individuals to prevent HIV infection. NIAID also is pursuing research in the development of next-generation interventions, such as broadly neutralizing antibodies; long-lasting injectable therapeutics; multipurpose prevention technologies (including microbicides); and a safe, effective HIV vaccine.

Antimicrobial resistance. NIAID plays an important role in the President's National Strategy for Combating Antibiotic-Resistant Bacteria (CARB) in collaboration with partners across the Federal Government. This year, NIAID will maintain and grow a robust antimicrobial resistance research portfolio to understand the mechanisms of resistance and to develop improved countermeasures. Key NIAID efforts include sequencing bacterial strains for the National Database of Resistant Pathogens; developing non-traditional therapeutics; optimizing current treatment strategies to reduce the emergence of drug resistance; and developing diagnostic platforms capable of detecting multiple resistant pathogens.

Influenza. NIAID influenza research aims to address the constant threat of seasonal influenza and the potential for pandemic influenza. In particular, NIAID is pursuing several promising universal influenza vaccine candidates that could protect against multiple influenza strains over multiple influenza seasons. In animal models, NIAID investigators have shown that two different universal influenza vaccine candidates can protect against numerous influenza strains. Both of these vaccine candidates, a nanoparticle vaccine and a virus-like particle vaccine, will be investigated for further development and clinical testing.

Malaria. NIAID research support contributed to the early stages of the development of the RTS,S vaccine, the first vaccine shown to protect against malaria in young children. In a recent study, NIAID-supported scientists used advanced genomic sequencing technology to help explain why the RTS,S vaccine is only partially effective. The researchers found that children infected with malaria parasites harboring genetic variants that did not match the protein targeted by the vaccine were less likely to be protected. These results will inform pilot implementation of the RTS,S vaccine endorsed by the World Health Organization as well as future malaria vaccine development strategies.

Tuberculosis (TB). NIAID is playing a critical role in accelerating basic and applied research to combat multidrug-resistant TB (MDR-TB) as part of the President's National Action Plan for Combating MDR-TB. With MDR-TB cases increasing worldwide, there is a need for new diagnostics to rapidly identify resistance, as well as biomarkers to determine whether a particular TB drug regimen is effective. NIAID scientists have identified two medical imaging technologies that may help predict TB drug treatment outcomes. Positron emission tomography and computed tomography images allow researchers to monitor the burden of bacteria remaining

in the lungs after therapy. These technologies potentially could be used in combination to quickly assess effectiveness of drug treatments and shorten the duration of clinical trials. NIAID also supports efforts to develop improved TB vaccines. NIAID research has contributed to more than half of the current clinical pipeline of TB vaccine candidates, and NIAID is working with product developers to transition promising candidates to advanced clinical trials.

Respiratory syncytial virus (RSV). RSV is a serious childhood respiratory infection. Each year in the United States, RSV causes an average of approximately 55,000 hospitalizations among children younger than 5 years. NIAID-funded researchers have developed a promising pediatric RSV vaccine candidate. Early tests in children and—adults show the vaccine is safe and elicits a stronger immune response than previously developed RSV vaccines. NIAID has launched an RSV human challenge model at the NIH Clinical Center to test the efficacy of this vaccine candidate in adults infected with RSV.

RESEARCH ON IMMUNOLOGY AND IMMUNE-MEDIATED DISORDERS

NIAID remains committed to advancing our understanding of the immune system and immune-mediated diseases. NIAID scientists and colleagues have created an extensive database of genetic information to facilitate research on immune disorders. These researchers used samples from twins to differentiate approximately 80,000 immune traits that are likely to be genetically regulated. NIAID has made this open-access resource available to researchers worldwide who are investigating diverse immune conditions.

NIAID research also has led to significant progress on treatments for immune-mediated diseases. NIAID-supported researchers continue to investigate findings from the groundbreaking Learning Early About Peanut Allergy (LEAP) food allergy study, which demonstrated that consumption of peanut-containing foods beginning in infancy decreased the development of peanut allergy in young children. The recent LEAP-ON trial demonstrated that tolerance to peanut persisted even after stopping peanut consumption for 1 year. This result suggests that early peanut consumption may be a viable long-term strategy for preventing peanut allergy. NIAID also is supporting research to improve current treatments for asthma. The Preventive Omalizumab or Step-up Therapy for Severe Fall Exacerbation (PROSE) clinical trial demonstrated that treatment with the antibody omalizumab reduced the number of seasonal asthma attacks experienced by inner-city children with a history of asthma attacks. Finally, NIAID continues to investigate treatment options for type 1 diabetes. An NIAID-supported clinical trial of the immune-suppressing drug alefacept in patients newly diagnosed with type 1 diabetes found that the drug helped preserve the function of insulin-producing cells in the pancreas. This effect persisted for more than a year after treatment ended.

CONCLUSION

NIAID continues to confront important historic public health challenges by supporting an established research portfolio in infectious and immune-mediated diseases while also responding rapidly to emerging infectious disease threats. NIAID has assisted international efforts to combat newly emerging and re-emerging pathogens, such as the Zika, Ebola, and dengue viruses. Research supported by NIAID also has advanced progress on persistent infectious and immune-mediated diseases worldwide. NIAID will continue to pursue effective medical countermeasures for these diseases in an effort to improve health globally in collaboration with U.S. and international government partners, academia, and industry.

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 2017 budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). NHLBI supports a large and diverse research portfolio including heart, lung, blood, and sleep (HLBS) disorders.

NHLBI has a proud history of translating Federal research funding into public health successes. There was a time in our Nation's history when a heart attack was known as a "widow-maker" and a childhood diagnosis of either sickle cell disease or cystic fibrosis was considered an early childhood death sentence. Thanks to medical breakthroughs enabled by NHLBI research investments, there has been a dramatic reduction in deaths from cardiovascular disease by 70 percent and children

born with sickle cell disease and cystic fibrosis have extended lifespans well into middle age. NHLBI has recently extended this legacy of funding major medical advances by conducting the Systolic Blood Pressure Intervention Trial (SPRINT) in patients with high blood pressure. This landmark study demonstrated that a more intensive treatment of high blood pressure prevents heart attacks, strokes, and heart failure while reducing death rates by 25 percent. SPRINT is the latest example of NHLBI's approach to turning discovery into better patient care outcomes. NHLBI's success serves as a compelling demonstration that a steadfast commitment to America's biomedical research enterprise yields a tremendous return on investment that enhances both the health and wealth of our Nation.

BUILDING ON SUCCESS TO ADDRESS NEW HEALTH CHALLENGES

Our past successes present new and compelling public health challenges that require strategic and timely investment in and by NHLBI. NHLBI's track record of success in keeping the Nation's blood supply safe in the face of the HIV/AIDS epidemic is proving to be a critically important foundation for building new initiatives that address the imminent threat to blood safety posed by the Zika virus. For example, NHLBI-supported investigators are developing ways to detect new and emerging microbes in donated blood and novel strategies to "sterilize" the blood prior to transfusion.

While we as a Nation must tackle emerging infectious disease outbreaks, we must remain vigilant in the fight against the greatest long-term public threat to our Nation's health and wealth—the growing epidemic and cumulative burden of chronic, age-related conditions such as cardiovascular disease, lung diseases, and vascular dementia. As we have reduced death from heart attacks, we must pivot to the emerging threat of heart failure—a chronic, debilitating, and costly complication of heart attacks—that millions of heart attack survivors must now face. While it is true that Americans have benefitted from high blood pressure treatments to prevent heart attacks and strokes, we must still address disorders such as vascular dementia—the second most common form of dementia and a major public health challenge for our aging population—that can develop as a result of cardiovascular diseases such as high blood pressure and stroke. To overcome the emerging health challenges of chronic HLBS disorders, which are major drivers of Medicare and Medicaid costs, it is critical to fund biomedical research to elucidate the underlying root causes and molecular mediators of these chronic conditions long before the disorder progresses to the end-stage of symptomatic debility and death. This is a moment of urgency in which investments in biomedical research could provide enormous return on investment by reducing medical care expenditures.

NHLBI funded discoveries are challenging the conventional viewpoint that chronic HLBS disorders are an intrinsic and inevitable consequence of the aging process. NHLBI is well poised to seize the scientific opportunities of today to advance research that can preempt or prevent chronic disease and overcome the economic and health challenges these disorders pose to millions of Americans. Our goal is to catalyze the next generation of discoveries and interventions designed to halt disease progression and promote the remission of chronic HLBS disorders. Not only do our existing and future research initiatives lay the foundation for mapping and therapeutically modulating biological pathways leading to chronic HLBS disorders, but they will help us understand how normal and diseased HLBS systems affect the health of or contribute to disease in other body systems.

PIONEERING PRECISION MEDICINE TO PREEMPT, PREVENT, AND PREDICT HLBS DISORDERS

Continued investment in NHLBI research will allow us to leverage new scientific discovery to realize personalized care for HLBS disorders. Scientifically aligned with NIH's Precision Medicine Initiative, the NHLBI Trans-Omics for Precision Medicine (TOPMed) program is pioneering a new integrated approach to understanding HLBS diseases by combining genetic, environmental, imaging, clinical, and other data from existing NHLBI-supported population-based studies and disease-based cohorts to create an accessible, communal data resource for scientific inquiry. The cohorts and studies in TOPMed represent a broad cross-section of the U.S. population in terms of racial, ethnic, and cultural backgrounds, as well as medical histories including common HLBS disorders such as atrial fibrillation, asthma, COPD, high blood pressure, obesity, and sleep apnea and rare disorders such as sickle cell disease and pulmonary fibrosis. TOPMed will integrate these genetic data with other data sets to allow researchers to study and define health and disease across the lifespan, uncover novel disease risk factors, and identify subtypes of disease that may be amenable to personalized treatment. These new discoveries will help reduce the

Nation's disease burden by increasing our capacity to preempt, prevent, and predict HLBS disorders.

For many HLBS disorders we do not know the molecular cause of disease, and we lack effective early markers for clinicians to detect disease in the earliest stages. The complex nature of HLBS disorders often involves changing dynamics within individual organs and between multiple body systems and changes across the lifespan due to normal genetic variation and common environmental exposures. The TOPMed program provides the opportunity to develop a large normative dataset to begin defining the transitions from normal to pre-, early-, and late-disease States.

Chronic Obstructive Pulmonary Disease (COPD) and pulmonary fibrosis are two diseases for which greater ability to recognize pre-disease States and early biomarkers can inform interventions to stop or even reverse early molecular changes, before the body has irreversibly begun down a path of developing lung disease. Current research through the TOPMed program and COPD cohorts has shed new light on how people with COPD respond differently to environmental factors such as tobacco smoke and has identified developmental and inflammatory pathways at the root of the different disease experiences. These studies identified lung function genes that are differentially expressed between control and COPD patients, which may make possible new COPD drug targets to reverse genetic signatures in some patients and prevent disease progression.

Expanding research in disease diagnosis, prediction, and refinement of disease subtypes will inform medical practice and help clinicians deliver personalized interventions, sometimes based on a patient's genetic makeup, that have been proven effective for a patient's disease subtype. For example, NHLBI funded Center for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases (CADET) found a genetic risk factor of pulmonary fibrosis that occurs in about 40 percent of patients with idiopathic pulmonary fibrosis. This discovery is driving new diagnostic test development to predict who may develop this form of idiopathic pulmonary fibrosis and drug development to counteract the effects of this genetic variation.

CHARTING A NEW VISION

NHLBI believes a robust, diverse, and engaged community is essential to overcoming our future public health challenges. NHLBI also strive to capitalize on the synergies created and leveraged by patient-centric care models and patient-driven movements. Over the past year, NHLBI has spearheaded several broad collaborative partnerships to connect scientists, policymakers, patients, and healthcare providers, in person and digitally, to meet people where they are to advance national public health missions and chart our course for the coming years.

In June 2015, our Sickle Cell Disease Forum engaged over 400 diverse community partners to understand their greatest needs in the area of sickle cell disease research. This Forum reviewed the current knowledge base, some of which NHLBI and our funded Centers of Excellence in Hemoglobinopathies have helped discover. While our eye is keenly focused on finding a future cure, possibly through adaptation of emerging gene editing techniques, the Forum also helped focus our attention on more immediate ways that NHLBI can significantly reduce the daily burdens and improve clinical health outcomes for patients with sickle cell disease. For example, NHLBI is committed to gaining higher clinical adoption rates of NHLBI's landmark study findings that hydroxyurea can reduce the risk of strokes in children with sickle cell disease. The 2014 Transcranial Doppler (TCD) With Transfusions Changing to Hydroxyurea (TWiTCH) Study confirmed with promising evidence that hydroxyurea works as well as blood transfusions to lower TCD velocities, a critical marker of stroke risk in very young children with sickle cell disease. Helping clinicians move beyond traditional transfusion-only treatment and increasing the use of hydroxyurea will allow us to realize a stroke-free generation of children. NHLBI's Sickle Cell Disease Implementation Consortium is facilitating research to assess how coordinated interventions that interweave the patient's home, work, and medical provider environments can improve the health and well-being of patients with sickle cell disease in the United States. Lastly, the Forum reinforced NHLBI's view that we are not an island and our global partnerships to research sickle cell disease in Sub-Saharan Africa and Brazil are instrumental to refining research and treatment development for Americans of African and Hispanic descent, who make up a large proportion of sickle cell disease cases in the United States.

Our Strategic Visioning Initiative was one of our most notable engagement successes this year. NHLBI undertook a crowdsourcing effort to engage patients, investigators, professional societies, and the broader NHLBI community in an inclusive and iterative process to shape scientific priorities and guide our funding strategies over the next decade. During this process, more than 1,000 ideas were submitted

and 42,000 votes were cast by 4,000 members of the community from all 50 States and 42 countries around the world. In alignment with NIH's strategic plan, the resulting NHLBI Strategic Research Priorities will be published in late spring 2016 and explore four major goal areas: normal biology and health, pathobiology and disease, clinical and translation research, and biomedical workforce and training. The strength of our Strategic Visioning process rests in the collective input of the entire HLBS community which helps to ensure that the research NHLBI supports continues to address the most important and timely scientific and public health questions related to HLBS disorders and that NHLBI strategically invests in research areas that critically require our facilitation.

CONCLUSION

NHLBI's portfolio, enhanced by our soon-to-be-released Strategic Research Priorities, addresses the enormous economic and health burdens of heart, lung, blood, and sleep disorders. Strategic NHLBI investments in critical challenges and unanswered research questions over the next decade will leverage past research and public health gains to help unlock the potential of precision medicine; strengthen existing and foster new public-private partnerships for quicker translation of research findings into new drugs, devices, diagnostics, and cures; and advance implementation science so existing and cutting-edge science can be adopted to improve health and reduce health inequities in the Nation.

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 2017 budget request for the Fogarty International Center (FIC) of the National Institutes of Health (NIH).

STRENGTHEN AND SUSTAIN THE BIOMEDICAL WORKFORCE

The cutting-edge scientific advances that improve public health are built on foundations of research capacity and rigorous training for future scientific leaders. Through its research and research training programs, FIC is supporting the best science where problems are most acute, facilitating research collaborations between the United States and international investigators and institutions, and training the next generation of scientists to address global health challenges. FIC's niche of investing in future global health research leaders extends the reach of research institutions and equips scientists in the United States and low- and middle-income countries (LMICs) to solve health problems that affect us all.

Addressing today's complex global health challenges requires a critical mass of first-class scientists who are well versed in regional health problems. To this end, FIC continues to support the training of early-career U.S. scientists at research centers in LMICs. Through programs like the International Research Scientist Development Award, FIC and its NIH partners provide experiences that encourage early-career U.S. investigators to take risks and approach problems creatively and collaboratively under constraints that may not exist in high-income settings. For example, Dr. Maria Hyoun Kim of Baylor College of Medicine is working with mentors in Malawi and the United States to improve prevention of mother-to-child transmission of HIV in LMICs. Specifically, her research evaluates Malawi's novel national Option B+ (B+) program, which offers lifelong antiretroviral treatment to HIV-infected pregnant and breastfeeding women, and will shed light on how effective B+ may be for preventing babies from becoming infected.

In addition, FIC has supported the training of thousands of scientists in LMICs who, with their intimate knowledge of the local context, are uniquely poised to make discoveries in global health research. Many of these investigators have become leaders in academic institutions and ministries of health in their home countries, and are involved in national efforts to improve the healthcare of the local population. For example, FIC's International Collaborative Trauma and Injury Research Training Program has expanded trauma and injury research partnerships between U.S. and LMIC scientists, and is generating data for evidence-based decisionmaking in injury-related clinical treatment and prevention programs. With support from this program, the University of California, Los Angeles, School of Medicine and the University of Cape Town in South Africa are working together to address the effects of sexual and physical violence during pregnancy on the growth and development of infants. Their study found that maternal exposure to physical violence in the year preceding delivery was significantly associated with lower birth weight in the in-

phants. Further research is planned to assess relevant underlying mechanisms and methods in the communities so that effective intervention plans and health policies can be developed for South Africa and other sub-Saharan African countries.

Past FIC investments have multiplied the number of foreign investigators working abroad who serve as change agents within their institutions, which are then positioned to participate in international scientific networks. For example, in partnership with the Office of the Global AIDS Coordinator at the Department of State, FIC administered the Medical Education Partnership Initiative (MEPI). MEPI provides medical education and research training for medical students, faculty, and other health professionals in sub-Saharan Africa. FIC is continuing to foster the next generation of researchers by providing training and mentored research opportunities specifically to junior faculty in MEPI-supported institutions. The MEPI Junior Faculty Program builds on MEPI's momentum and existing platform to continue expanding research capacity of junior faculty from MEPI institutions. This second-generation program is increasing retention of faculty who will focus on evidence-based clinical teaching as well as strengthen international research collaboration.

RESEARCH

Research supported by FIC's programs is generating critical scientific evidence that can lead to new diagnostics, prevention and treatment strategies. FIC's Global Brain Disorders Research (Brain) program has energized a global health research agenda around brain and nervous system diseases and disorders. In collaboration with several NIH Institutes and Centers (ICs), Brain has catalyzed innovations relevant across the lifespan, from fetal and neonatal neuro-development to neurodegenerative diseases of later life, such as Alzheimer's disease. For example, scientists at Albert Einstein College of Medicine are collaborating with colleagues in India to investigate cognitive decline in older adults. Recent findings report prevalence of motoric cognitive risk syndrome (MCR)—a newly described predementia syndrome—and identify MCR in older adults as a strong, early risk factor for cognitive decline that can be used to identify seniors at high risk for dementia.

Over the next 5 years, FIC's Global Environmental and Occupational Health Hub Program will support the establishment of seven regional research and training hubs. Each hub is based in an LMIC and consists of a multidisciplinary group of researchers and partner organizations who will collaborate on common research and training topics that address environmental and/or occupational health issues. For example, one hub in Thailand is investigating pesticides commonly used in agriculture across Southeast Asia, to see if they act as endocrine disrupters, increasing the risk of metabolic syndrome and associated diseases such as diabetes, stroke and heart disease. Another hub, in Peru, aims to build scientific capacity and support research on air pollution and climate change, with links to the neighboring countries of Ecuador, Bolivia and Chile.

FIC is stimulating innovation in the development and implementation of technologies and other locally relevant solutions to address global health problems. In an effort to understand the impact of mobile technologies on health, FIC's Mobile Health: Technology and Outcomes in LMICs (mHealth) program supports research on the use of mobile devices to generate better health outcomes. One such example is a team of U.S. and South African scientists that are developing a mobile screening tool to be used by staff with minimal training to detect neurocognitive impairment resulting from HIV infection. Pioneering tools like this can improve care, reduce costs, and have potential relevance for the United States and worldwide.

FIC's mathematical modelers have been at the forefront of addressing the recent Zika and Ebola outbreaks. Researchers at FIC are utilizing a novel methodology to analyze Internet news reports on Ebola from Africa to describe pathways of transmission. This methodology provided evidence that news reports can be a useful source of epidemiologic data. Researchers supported in part by FIC also are predicting the international spread of Zika virus in Brazil due to the August 2016 summer Olympic Games; these research findings were recently published in the *Lancet* in January 2016.

OTHER

FIC leverages partnerships to maximize the impact of NIH investments globally. The Global Network for the Study of Malnutrition and Enteric Disease (MAL-ED) is an international collaboration of investigators led by FIC and the NIH Foundation. Established in late 2008, the multi-year, multi-site project is supported by the Bill & Melinda Gates Foundation. The goal of MAL-ED is to investigate the interactions among exposure, infection, and disease associated with enteric pathogens; diet and nutritional status; and, socio economic status in relation to resulting im-

pacts on gut physiology; immune function and vaccine response; physical growth; and, cognitive development. A prospective field, clinical, and laboratory based observational study of cohorts of neonates followed to 24 months has been established at geographically diverse sites in Asia, Latin America, and sub-Saharan Africa. The findings of such analyses will be applied toward improving long-term public health in resource-poor settings.

Over the last few years, the emerging economies of Brazil, Russia, India, China and South Africa (BRICS) have built highly capable biomedical enterprises. NIH and BRICS countries are establishing innovative partnerships, funding individual teams of experts who work together sharing expertise to speed discovery. NIH is partnering with the Brazilian State of São Paulo's Science Foundation (FAPESP) to parallel-fund U.S.-São Paulo R01 applications that are meritorious in standard NIH peer-review. FIC developed and is implementing the program, which calls for FAPESP to fund the Brazilian institution while NIH funds the U.S. institution. To date, 22 NIH ICs have signed on, covering most research areas across NIH. Another example is the United States-China Program for Biomedical Research Cooperation, a 2010 bilateral agreement that FIC helped draft and facilitate, that strengthens and develops cooperation in basic biomedical research. In this program, NIH provides funding to support U.S. scientists involved in the research collaborations, while the National Natural Science Foundation of China (NSFC) provides funding to support the Chinese scientists. So far, there have been a total of 109 awardees, addressing scientific questions in the areas of cancer, infectious diseases, neurological diseases, and mental health.

CONCLUSION

FIC will continue to invest in the most promising minds in global health research, strengthen the capacity of research institutions to be sustainable platforms for cutting-edge science, and catalyze meaningful international scientific collaborations in fiscal year 2017 and the years to come.

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 2017 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. We achieve this mission by supporting research to: promote health and prevent disease; advance symptom science to develop personalized health strategies; enhance self-management of chronic conditions; improve end-of-life and palliative care; develop new technologies to improve health; and train nurse scientists. This year, we are pleased to commemorate NINR's 30th anniversary, which provides an opportunity to reflect on many of the accomplishments being made every day by nurse scientists across the Nation. In October 2015, NINR hosted the first in a series of scientific events to highlight significant contributions of nursing science for improving health. As we envision the next 30 years, we are confident that NINR's support of nursing research will continue to improve the lives of diverse individuals, families, and communities across the life span. I am grateful for this opportunity to share with you some examples of the innovative research that NINR supports.

IMPROVING THE HEALTH OF CHILDREN AND ADOLESCENTS

Chronic conditions such as asthma, obesity, and diabetes have the potential to negatively affect the quality of life of children and adolescents. NINR-supported scientists are addressing this issue by developing innovative interventions to increase positive health outcomes in children. NINR-supported researchers demonstrated the effectiveness of a school-based healthy lifestyles program for overweight/obese and depressed teens. Results showed that a year after completing the program, there was a significant decrease in the proportion of overweight and obese students, and students who had begun the program with severely elevated depressive symptoms had significantly lower depression.

NINR maintains its commitment to support research to improve health for children from vulnerable groups who are often disproportionately affected by chronic conditions. One recent NINR-supported study showed improvements in asthma epi-

sode management and prevention behaviors in medically underserved, inner-city school-age students who received a school and community based asthma health education and counseling program. In other ongoing efforts, NINR-supported investigators are testing a community-based participatory intervention aimed at American Indian/Alaska Native teens and their mothers to raise awareness of the risks of gestational diabetes mellitus, promote a healthy lifestyle, and prevent subsequent development of type 2 diabetes.

MAINTAINING HEALTH IN OLDER ADULTHOOD

In light of our rapidly aging population, it is more important than ever to support efforts to prevent chronic illness early in life and to promote active lifestyles, health, and independence as people age. One promising area of research focuses on developing new technologies to improve and maintain physical mobility for older adults. For example, NINR-supported researchers designed an innovative unpowered ankle exoskeleton that harnesses the power of a person's own muscles to make walking more efficient. Although scientists are still developing and testing the exoskeleton, it has the potential to make walking easier for people recovering from an injury or dealing with normal aging issues. Another recent NINR-led initiative focuses on development of technological and biobehavioral interventions to help persons with dementia or cognitive impairment maintain independence and quality of life, as well as to reduce stress and burden on caregivers. NINR-supported researchers are also uncovering complex relationships among biological, physical, and behavioral factors that may play a role in depressive symptoms in older adults. A recent study revealed that mutations in a gene known to be related to depression, as well as pain, fear of falling, and low physical activity, were all associated with depressive symptoms in older adults. NINR is also leading an initiative to support prevention research in mid-life adults, which will inform efforts to optimize health and wellness as people age.

ENHANCING END-OF-LIFE AND PALLIATIVE CARE

As the lead NIH Institute for end-of-life research, NINR supports research to identify the most effective strategies to ease the symptoms of advanced illness and to assist families in making difficult end-of-life decisions. In an effort to build the science of end-of-life and palliative care, we continue to support a palliative care research cooperative (PCRC), which brings together multidisciplinary researchers from universities, health systems, hospices, and hospitals across the United States. Recent findings from research supported by the PCRC revealed that discontinuing statin medication use in patients with advanced illness is safe and may increase quality of life, decrease the use of non-statin medications, and reduce costs. In 2015, NINR launched the second phase of NINR's Palliative Care: Conversations Matter® initiative, which focuses on children, parents, and families, and includes a new brochure, in English and Spanish, to help raise awareness of the benefits of palliative care. NINR also is leading a new initiative to support research to better understand the unique perspectives, needs, wishes, and decisionmaking processes of youth living with serious illnesses and their families, and to enhance their quality of life.

LOOKING TOWARD THE FUTURE: NURSE SCIENTISTS

One of NINR's fundamental goals is to develop the next generation of nurse scientists to address the Nation's most pressing health issues. NINR offers a variety of training opportunities to nurse scientists and trainees at all career levels, and recognizes the importance of supporting new investigators whose success is so critical to the future of innovative research and high-quality healthcare. In order to build a scientific workforce that is innovative, diverse, and ready for the future, NINR's training programs provide nurse scientists with the skills and tools to support continued advancements in science and improvements in health. For example, in 2015, NINR sponsored our second Big Data Research Boot Camp at NIH, a week-long intensive training that provides a foundation in big data science methodologies and strategies for incorporating new methods to strengthen research proposals. NINR's Summer Genetics Institute is an intensive program for graduate students, faculty, and clinicians designed to provide a foundation in molecular genetics to improve research and clinical practice.

CONCLUSION

Thank you for this opportunity to share some of NINR's accomplishments and the important work being done every day by nurse scientists across the country. NINR

will continue to support innovative research to improve health now and in the future.

PREPARED STATEMENT OF ERIC 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 2017 budget request for the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH).

This past October, the scientific community celebrated a quarter century since the launch of the Human Genome Project. Now, roughly 13 years since the successful completion of that landmark effort, NHGRI looks forward to the next quarter century of genomics and its applications to advance human health. To this end, NHGRI is fostering a continuum of research from basic studies of the structure and function of genomes to work that advances medical science and seeks to improve the effectiveness of healthcare. Research funded by NHGRI, especially in the area of genomic medicine, has laid the foundation for major transformational efforts, such as the Precision Medicine Initiative and the National Cancer Moonshot.

As an example, NHGRI's partnership with the National Cancer Institute in leading The Cancer Genome Atlas for nearly 12 years has led to powerful new insights that will fuel the National Cancer Moonshot. Through the use of new genome-analysis technologies, data have been generated for over 10,000 tumor specimens, allowing the assembly of a rich data resource that is now freely available to any qualified researcher. This body of work is providing new insights about classifying and treating cancer, fundamental information for the National Cancer Moonshot.

Another major research program supported by NHGRI, the 1000 Genomes Project, has now established a powerful data resource with information about how humans differ with respect to their genomic blueprint. With its final summary papers published in *Nature* this past October, this international effort analyzed the genomes of over 2,500 people from 26 populations around the globe, identifying and cataloguing more than 88 million places in the genome that humans differ. Together, the generated information accounts for more than 99 percent of the common genomic variants (or 'spelling differences') that exist in the human population. By producing a global catalog of human genomic variation, researchers can now focus on which of the identified variants play a role in health and disease.

Despite the remarkable progress in genomics over the past quarter century, more powerful and accessible approaches for studying genome structure and function are needed. To help address this need, the Centers of Excellence in Genomics (CEGS) program supports multi-investigator, interdisciplinary teams that develop new approaches and technologies for using genomics in biomedical research. fiscal year 2017 funds for NHGRI will support CEGS efforts that combine genome-editing technologies and tissue-engineering methods to develop improved models of complex tissues such as the brain. The CEGS program exemplifies how basic research can be applied to specific problems, yielding solutions that can advance diverse fields of inquiry.

The promise of genomics as a clinical tool for improving patient care is now coming into focus. A program that vividly highlights this capability is the Undiagnosed Diseases Network (UDN). An extension of the Undiagnosed Diseases Program launched within the NIH Intramural Research Program in 2008 and funded by the NIH Common Fund, the UDN embodies the promise of genomic and precision medicine. Under NHGRI's leadership, both programs are helping patients (and their families) that have faced diagnostic odysseys and are discovering the genomic bases of extremely rare disorders. The value of UDN is multifaceted, with some aspects related to the care and support it provides to its patients and other aspects related to robust approaches being developed for the study of rare medical conditions. fiscal year 2017 funds for the program will support an expansion in patient enrollment across the national network.

NHGRI is further maximizing the potential for public benefit from the Federal investment in genomics with programs such as UDN by promoting synergy across research communities. Leveraging leading experts across national consortia directly stimulates dialog and an exchange of ideas that can prove mutually beneficial to all groups involved. An illustration of this can be seen with the collaboration between UDN and NHGRI's Centers for Mendelian Genomics program, a large-scale effort that is elucidating the genomic causes of rare human diseases. Through their synergistic interactions, these consortia are producing new insights about basic biological pathways that are relevant to both rare diseases as well as more common ones. Utilizing the discoveries emanating from rare disease studies should propel forward

basic understanding of common diseases, particularly in the characterization of disease mechanisms and the establishment of new treatment options.

NHGRI also recognizes the importance of examining and addressing the ethical, legal, and social issues associated with moving genomics initiatives forward and with implementing genomic medicine. In fiscal year 2017, NHGRI will thus continue to fund research that examines the increasing accessibility of genomic information and technologies within society. Such studies will investigate questions related to biobanking, clinical genome sequencing, and broad data sharing—all issues of great relevance to the Precision Medicine Initiative. A particular focus will be placed on how such issues affect studies involving vulnerable or underrepresented populations. Genomic privacy and genetic discrimination, as well as the complexities associated with the return of results from genomics research studies, will also be explored.

Educating providers, patients, and the public about genomics is also imperative for the successful incorporation of genomics into healthcare. NHGRI dedicates significant time and attention to outreach efforts and the education of various stakeholders. The highly successful Genome: Unlocking Life's Code exhibition, developed in conjunction with the Smithsonian Institution, has now been seen by more than four million people as it travels to cities big and small across the United States.

NHGRI's well-rounded portfolio of basic, translational, and clinical research programs has the long-term aim of using genomics to advance the health of all Americans. Fiscal year 2017 funds will help to ensure that NHGRI continues to lead the genomics community, support the broader biomedical research community, and help realize a future of remarkable genomics-enabled healthcare innovations.

PREPARED STATEMENT OF BETSY L. HUMPHREYS, ACTING DIRECTOR, NATIONAL
LIBRARY OF MEDICINE

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2017 budget request for the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

OVERVIEW

NLM, the world's largest medical library, is the most visible face of NIH across the United States and around the globe. Through its information systems, a cutting-edge informatics research portfolio, extensive training programs, and many partnerships, NLM plays an essential role in catalyzing and supporting the translation of basic science into new treatments, new products, improved practice, useful decision support for health professionals and patients, and effective disaster and emergency preparedness and response. NLM coordinates a 6,400 member National Network of Libraries of Medicine (NN/LM) that provides a field force for improving access to high-quality health information in communities nationwide, with an emphasis on populations with health disparities.

Millions of scientists, health professionals, and members of the public use NLM's electronic information sources billions of times each year. The range of information that NLM organizes and disseminates is enormous, including genetic, genomic, and biochemical data; images; clinical trials; published and unpublished research results; historical archives; decision support resources; scientific and health data standards; informatics tools for system developers; and health information for the public. Every day, researchers submit 5 terabytes of data to NLM databases and users download more than 50 terabytes. Anyone can search or download information directly from an NLM website, find it via an Internet search engine, or use an "app" that provides value-added access to NLM data. Thousands of commercial and non-profit system developers regularly use the applications programming interfaces (APIs) that NLM provides to fuel private sector innovation and to embed access to NLM information services within electronic health records (EHRs).

NLM actively conducts and supports basic research in computational biology and informatics and also funds development of computational tools and methods for analysis of scientific data, electronic health records, images, and publications. In fiscal year 2015, NLM intramural scientists were key members of an international CRISPR-Cas research team that identified three new naturally occurring systems that show potential for genome editing.

BIOMEDICAL AND HEALTH INFORMATION SERVICES

In fiscal year 2015, NLM greatly expanded the quantity and range of high-quality information readily available to scientists, health professionals, and the general

public. For example, more than 806,000 new journal articles were indexed for PubMed/MEDLINE, NLM's most heavily used database, which contains more than 25 million references to articles in the biomedical and life sciences journals, with links to related scientific data and full-text articles on publishers' websites and in NLM's PubMed Central (PMC) repository. PMC now includes more than 3.6 million full-text research articles, including those submitted in accordance with the NIH Public Access Policy and similar policies of the Department of Health and Human Services (HHS) and several other Federal agencies.

NLM's National Center for Biotechnology Information (NCBI) is a leader in and a hub for the international exchange of big data utilized in molecular biology, genomics, and clinical and translational research. Some of the largest datasets are available in the cloud to facilitate access and analysis by researchers who have insufficient bandwidth or computing power. In fiscal year 2015, the database of Genotypes and Phenotypes (dbGaP), which connects individual-level genomic data with individual-level clinical information, grew by more than 20 percent and now contains 600 studies involving more than one million people. The RefSeq database of curated reference sequences grew to nearly 15 million genomic records, an 88 percent increase, and more than 51 million protein records from over 54,000 organisms. Many NLM databases, including dbGaP, RefSeq, the Genetic Testing Registry, and ClinVar, are fundamental to the identification of important associations between genes and disease, and to the translation of new knowledge into better diagnoses and treatments.

NCBI continues to collaborate with the Food and Drug Administration (FDA), Centers for Disease Control and Prevention, the Department of Agriculture, and other groups to maintain a database of whole genome sequencing (WGS) data for antibiotic-resistant bacteria along with tools to facilitate analyses of such data. The database provides an important resource for surveillance and research into the mechanisms underlying the emergence of antibacterial resistance. This program builds upon a successful collaborative project among these same agencies to use WGS to more quickly and accurately identify and investigate outbreaks of disease caused by foodborne bacteria.

ClinicalTrials.gov, the world's largest clinical trials registry, now includes more than 200,000 registered studies in 190 countries and summary results for more than 18,700 trials, including many not available elsewhere. When finalized, regulations to implement the Food and Drug Administration Amendments Act of 2007 and a proposed NIH clinical trial reporting policy are expected to further increase the amount of information submitted each year to this valuable resource.

NLM's MedlinePlus provides access to high quality consumer health information produced by NIH and HHS agencies, other Federal agencies, and authoritative private organizations. It also serves as a gateway to specialized NLM information sources for consumers, such as the Genetic Home Reference and the Household Products Database. Available in English and Spanish, with selected information in 40 other languages, MedlinePlus averages more than 1.6 million visits per day.

In fiscal year 2015, NLM collaborated with the HHS Assistant Secretary for Preparedness and Response and the National Institute of Environmental Health Sciences to develop new information resources for pre- and post-disaster health issues and disaster research response.

ELECTRONIC HEALTH RECORDS AND CLINICAL DATA ANALYSIS

For more than 40 years, NLM has supported seminal research in biomedical informatics, including EHRs, imaging, clinical decision support, and health information exchange. It has also been the principal funder of university-based programs that have trained many of today's leaders in informatics research and health information technology. As adoption and deployment of EHRs increases, so do opportunities to mine increasingly large stores of patient data for research and public health. NLM conducts and supports research to enable effective use of EHR data in knowledge discovery, public health surveillance, and healthcare quality improvement. In fiscal year 2015, NLM intramural scientists took advantage of the Centers for Medicare and Medicaid Services' (CMS) efforts to streamline research access to Medicare data to conduct studies about epidemiology of drug-drug interactions and the potential association between Simvastatin use (a drug used to lower cholesterol and triglycerides) and dementia/Alzheimer's disease.

In close collaboration with the HHS Office of the National Coordinator for Health Information Technology and with assistance from CMS, Veterans Health Administration, and FDA, NLM develops, funds, and disseminates the clinical terminologies designated as U.S. standards for meaningful use of EHRs and health information exchange. NLM produces a range of tools that help EHR developers and users to

implement these standards and makes them available in multiple formats, including via APIs. NLM's technical and financial support enables clinical terminology standards to be updated regularly to reflect new drugs, tests, devices, and changes in medical knowledge and health practice—and also allows them to be used free-of-charge in U.S. healthcare, public health, biomedical research, and product development.

The inclusion of standard terminology in EHRs enables more effective clinical decision support by making it easier to use information in a patient's record to retrieve knowledge relevant to that record. In fiscal year 2015, NLM's MedlinePlus Connect service increased its utility to EHR vendors seeking to connect their products directly to NLM's high quality information relevant to a patient's conditions, medications, and test results by expanding its links to standard terminologies and billing codes. Standardized EHRs are also an increasingly important source of data for cost-effective observational, clinical, and translational research and will enhance the value of the Precision Medicine Initiative cohort. NLM continued its work to facilitate the inclusion of standard clinical terminology in common data elements and patient assessment instruments used in NIH and HHS-funded comparative effectiveness and clinical research. NLM's Unified Medical Language System (UMLS) resources provide essential infrastructure for advanced clinical decision support by connecting standard clinical terminologies to billing codes and more than 120 other important biomedical vocabularies, such as those used in information retrieval and gene annotation. By linking the many different terms used to represent the same concepts and by providing associated natural language processing programs, NLM's UMLS resources help computer programs interpret biomedical text correctly. These resources are heavily used in NIH-funded research; in commercial product development; and in many electronic information services, including those produced by NLM.

REACHING THE PUBLIC

NLM has a range of programs to enhance awareness and use of NLM's information services among biomedical researchers, health professionals, librarians, patients, and the public. NLM works closely with more than 6,300 members of the NN/LM—academic health sciences libraries, hospital libraries, public libraries, and community-based organizations—and through formal partnerships with historically black colleges and universities, tribal colleges, and other minority serving institutions. In fiscal year 2015, dozens of community-based projects were funded across the country to enhance awareness and access to health information, including in disaster and emergency situations, and to address health literacy issues. Use of mobile sites, “apps,” APIs, and responsive design techniques help NLM tailor the delivery of content to the range of devices employed by its users.

NLM is redesigning many of its web interfaces so that the information display adjusts automatically to the size of the device, including smart phones. In fiscal year 2015, the Library released new “responsive design” versions of MedlinePlus and MedlinePlus en español. NLM continues to be a leading player in social media amongst HHS agencies with active Facebook, Twitter, Flickr, Pinterest, and YouTube accounts; several online newsletters; and its NN/LM, which covers the U.S. and hosts eight Facebook pages, nine Twitter feeds, and 12 blogs. NLM is consistently ranked among the most liked, most followed, and most mentioned organizations amongst small government agencies with social media accounts.

In conclusion, NLM is a trustworthy source of health information for the public and vital to the practice of 21st Century medicine and the progress of science. NLM's information services and research programs serve the Nation and the world by supporting scientific discovery, clinical research, education, healthcare delivery, public health response, and the empowerment of people to improve personal health. NLM is committed to the development and use of innovative computing and communications systems to enhance access to the results of biomedical research.

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 2017 budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH).

As the primary Federal agency supporting medical research on diseases of the bones, joints, muscles, and skin, NIAMS touches the lives of nearly every American. Arthritis limits the activities of more than 22.7 million adults in the United States

each year (National Health Interview Survey, 2010–2012); medical care and lost wages attributable to musculoskeletal conditions cost Americans \$874 billion annually (Agency for Healthcare Research and Quality Medical Expenditures Panel Survey, 1996–2011); and skin conditions such as eczema and psoriasis affect more than 12 percent of people worldwide (Global Burden of Disease Study, 2010). NIAMS is working to enhance health, lengthen life, and reduce illness and disability by supporting basic, translational, and clinical research that will make a difference for patients; fostering innovation to meet current research needs and to support the next generation of biomedical researchers; and enhancing stewardship, while reducing administrative burdens on researchers.

BASIC RESEARCH LEADS TO NEW UNDERSTANDING OF DISEASE

NIAMS investments in basic research are uncovering the underlying mechanisms of biological systems and providing new understanding of the basis of disease. For example, NIAMS intramural researchers, as part of an international consortium, analyzed DNA from nearly 1,000 children with systemic juvenile idiopathic arthritis, a severe form of childhood arthritis. The researchers showed that changes in a section of the genome related to immune cell function are strongly associated with an increased risk of developing the condition; when combined with other knowledge about the gene region involved, the finding suggests that defects in both how the body immediately reacts to infection, and how it adapts over time, contribute to the disease.

Long-term investments in data resources to facilitate basic science discoveries continue to produce results. One such resource, the Osteoarthritis Initiative, was established a decade ago as a repository for medical images, clinical data, and biospecimens from people who were at high risk of developing knee osteoarthritis. Recently, researchers mining the publicly available database found joint changes that may predict who will go on to develop osteoarthritis. This discovery is calling into question long-held beliefs about how osteoarthritis arises and may open new avenues for halting joint disease at its earliest stages.

Basic research on fundamental biological processes in healthy tissues could of regeneration, and currently, we know little about the signaling pathways that are involved. NIAMS-supported researchers are beginning to uncover the basic molecular events that underlie recovery of certain tissues, such as hair follicle regeneration after skin wounding. Recently, two key regulators of this process were identified in mouse models. Interestingly, both of the molecules are also involved in immune system functions, such as protection against viral infections. By understanding regeneration in this model, scientists may one day be able to develop methods to stimulate repair of other human tissues. In fiscal year 2017, NIAMS plans to provide funding for small businesses to develop novel complex 3-dimensional (3-D) in vitro human musculoskeletal and skin tissue models. These models will facilitate the study of human tissue physiology and pathophysiology, and potentially lead to better interventions that prevent or cure diseases.

BIOMARKERS—A TOOL FOR DISCOVERY AND CLINICAL CARE

Biomarkers are measurable biological or chemical indicators of health or disease that are accurate and reproducible. NIAMS research to identify, validate, and utilize biomarkers across the spectrum from basic to clinical research is bearing fruit. In a recent study, NIAMS intramural researchers examined the blood of patients with ANCA-associated vasculitis (AAV), a systemic autoimmune disease that causes inflammation in the blood vessels. The researchers found that the amount of a distinct type of white blood cell in patients with vasculitis correlated with how they would respond to treatment. Once validated, this discovery could inform clinicians if a particular patient is likely to respond to an intervention, helping them to tailor treatment to the individual.

In addition, biomarkers are important tools in monitoring disease status. Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle weakness, and biomarkers that distinguish among stages of the disease could enable researchers to rapidly assess how well a novel intervention is working. NIAMS-supported investigators have identified several different types of biomarkers for DMD using new techniques to monitor changes in muscle quality. Recently, other researchers found dozens of proteins in blood that were significantly different between DMD patients and individuals without the disease. Several of these proteins also changed during progression from early disease to its later stages. In the future, this information may help researchers develop new interventions, identify appropriate candidates for clinical trials, and more rapidly interpret trial results.

Other biomarkers are being evaluated as surrogate outcomes when examining new interventions for diseases. For example, NIAMS-supported researchers tested a new drug to prevent scarring in patients with systemic sclerosis, a severe form of the chronic connective tissue disease scleroderma. The researchers showed that the drug significantly reduced the amount of two proteins in the skin of patients, and these reductions correlated with improvement in skin condition assessed via traditional clinical measures. The study results demonstrate the value of a biomarker-based approach to measuring treatment response and confirming clinical data.

HELPING CLINICIANS BETTER CARE FOR PATIENTS

While basic research into the underlying mechanisms of disease will always be an important focus, NIAMS research also helps ensure that physicians have up-to-date information to facilitate treatment decisions based on the current state of the science. For example, children with an abnormal curvature of the spine, called adolescent idiopathic scoliosis (AIS), often are instructed to wear braces to prevent worsening of the curve, but the effectiveness of this treatment had not been rigorously tested. In 2007, NIAMS-supported investigators launched the Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST) to compare the risk of curve progression in tweens and teens with AIS who wore a brace versus those who did not. In January 2013, the trial was stopped early after finding that bracing significantly reduced the risk of curve progression and the need for surgery, and that more hours of brace wear were associated with higher success rates. These results were the primary reason several healthcare provider organizations recently updated their recommendations regarding scoliosis screening for adolescents. In addition, the United States Preventive Services Task Force is currently revisiting its screening recommendations for AIS.

NIAMS researchers are also leveraging existing data to aid physicians in everyday practice. Recently, NIAMS intramural scientists conducted a comprehensive review of clinical studies into the various treatments available for two major causes of back pain, ankylosing spondylitis and non-radiographic axial spondyloarthritis. Based on the systematic review, a series of treatment recommendations were developed, and they have been endorsed by the American College of Rheumatology. The recommendations provide clinicians with the current best-evidence for the treatment of these common conditions, and may facilitate the effective use of healthcare resources, reduce inappropriate care, and minimize variation in care.

Looking to the future, NIAMS will capitalize on prior investments and recent advances in the science of patient-reported outcomes (PROs) to improve the health and well-being of pediatric patients. The Patient Reported Outcomes Measurement Information System, or PROMIS®, was an NIH Common Fund project, co-led by NIAMS, to develop a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being. The PROMIS tools can give physicians a clearer understanding of how the patient is feeling and functioning, and can be used across a wide variety of chronic diseases and conditions in both research settings and in routine care. In fiscal year 2015, NIH funded the Validation of Pediatric Patient-Reported Outcomes in Chronic Diseases (PEPR) Consortium that will expand existing and new PRO tools for pediatric patients, ultimately improving the treatment of chronic diseases in children. PEPR is part of a trans-NIH effort to lay the foundation for a new multi-year initiative called the Environmental Influences on Child Health Outcomes (ECHO) program set to begin in fiscal year 2017.

FOSTERING INNOVATION AND ENHANCING STEWARDSHIP

NIAMS is actively working to enhance and strengthen our scientific stewardship and encourage innovation. As part of these efforts, NIAMS is supporting several programs targeting the next generation of researchers. In fiscal year 2015, NIAMS launched a new program called the Supplements To Advance Research from Projects to Programs, or STAR, awards. STAR promotes innovation and exploration of high-risk ideas by providing flexible funding to early established investigators to expand upon their currently funded project and facilitate transition from a single project to a research program. NIAMS made three STAR awards in fiscal year 2015, and anticipates another group of awards in fiscal year 2016.

In addition to STAR, NIAMS has implemented several programs to support clinical researchers, a vital population that faces unique challenges in pursuing research careers. Since fiscal year 2012, NIAMS has hosted an annual career development forum for extramural researchers who have received either a mentored clinical scientist development (K08) or patient-oriented research (K23) grant. The forum

provides awardees with opportunities to network with each other, as well as NIAMS leadership and program, review, and grants management officials; and enhances the Institute's support of early-stage physician-scientists by encouraging and enabling awardees to continue performing basic, translational, or patient-oriented research in their chosen fields. In addition to the forum in fiscal year 2016, NIAMS will implement a new trans-NIH policy of increased salary support for these same K awardees, a year earlier than required by NIH. Finally, NIAMS is planning a new small grant program to assist early-stage clinician scientists as they pursue research independence through the so-called K-to-R transition, a particularly vulnerable period for investigators. Together, these and other training and fellowship programs will help ensure a robust pipeline of new investigators in the rheumatic, musculoskeletal, and skin disease mission areas.

NIAMS is also encouraging innovation and stewardship by collaborating with the research community and other stakeholders to elaborate on exciting new research opportunities. For example, NIAMS, on behalf of NIH, led the development of a new Action Plan for Lupus Research, and also participated in the development of the Action Plan for the Muscular Dystrophies. Both plans represent a synthesis of NIH internal input, as well as significant external input from the scientific, clinician, and patient advocacy communities. They will help to inform priority-setting processes among all interested organizations—Federal, private, and non-profit—and may inspire individual investigators as they develop innovative, independent research proposals. In addition, NIAMS is leading the Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus (AMP RA/Lupus). This unique public-private partnership with NIH, pharmaceutical companies, and non-profit organizations aims to transform the model for identifying and validating promising targets for the development of new drugs and diagnostics. The AMP RA/Lupus program was funded in late fiscal year 2014, and researchers and other partners have developed a research plan with distinct milestones. Substantial progress has already been made incorporating cutting edge technologies and establishing standard operating procedures that the broader scientific community will be able to leverage in the future.

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

Mr. Chairman and Members of the Subcommittee: I am pleased to present the President's fiscal year 2017 budget request for the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the National Institutes of Health (NIH).

Alcohol misuse has profound, adverse effects on individuals, families, and communities. Seventeen million people in the United States have alcohol use disorder (AUD), and the Centers for Disease Control and Prevention estimates that excessive alcohol consumption cost the United States \$249 billion in 2010. NIAAA is grateful for the increase to the NIAAA budget provided in fiscal year 2016. This additional investment will allow NIAAA to increase support for research training and career development programs, fund additional cutting-edge alcohol research projects, and facilitate the translation of alcohol research into practice.

AUD is a chronically relapsing brain disease. As individuals progress from initial alcohol use to risky drinking to AUD, changes occur in the structure and function of their brains. These changes perpetuate drinking and persist long after a person stops. A major focus of NIAAA's work is to develop a more thorough understanding of how these changes contribute to the development and maintenance of AUD. With the additional funding provided to the agency in fiscal year 2016, NIAAA is able to pursue several important new areas of inquiry in the neurobiology of alcohol misuse and AUD, including studies of the effects of adolescent drinking on brain development, exploration of neuroimmune function in the development of AUD, and identification of new AUD treatment targets.

Alcohol consumption during pregnancy can have devastating effects on the developing embryo and fetus. Fetal alcohol spectrum disorders (FASD), an umbrella term for a range of developmental, cognitive, and behavioral problems caused by prenatal alcohol exposure, are the leading preventable causes of birth defects and developmental abnormalities in the United States. NIAAA supports research on the mechanisms through which alcohol disrupts prenatal development, to develop new biomarkers to improve detection of drinking during pregnancy, to improve FASD diagnosis and establish more precise prevalence estimates in the United States, and to develop effective interventions to mitigate the adverse effects of prenatal alcohol exposure.

Adolescents are particularly vulnerable to the adverse effects of alcohol. Drinking during adolescence can impair the development of the frontal cortex, the region of

the brain responsible for executive function and decisionmaking; compromise short- and long-term cognitive functioning; and increase risk for alcohol problems later in life. NIAAA supports a broad portfolio of research to identify the factors that contribute to adolescent alcohol misuse and the effects of alcohol on the developing adolescent brain. The NIAAA-funded National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), for example, is a nationally-representative, longitudinal study evaluating brain structure and function in more than 800 youth before and after they start to drink. Building on NCANDA, NIAAA, along with other NIH Institutes and Offices, launched the Adolescent Brain Cognitive Development (ABCD) Study in September 2015. The study will recruit approximately 10,000 children ages 9–10, most of whom will not have initiated substance use, and followed into early adulthood. Participants' exposure to alcohol and other drugs (alone and in combination), academic achievement, cognitive skills, mental health, and brain structure and function will be tracked over a 10-year period. The findings will enable researchers to better understand the myriad factors that contribute to brain and cognitive development and how alcohol and other drugs affect these processes, and they will inform prevention and treatment interventions and public health strategies.

Like adolescents, young adults are also highly vulnerable to the adverse effects of alcohol misuse, and binge drinking is a particular concern within this population. In September 2015, NIAAA released its College Alcohol Intervention Matrix, CollegeAIM, an evidence-based decision tool to help college and university administrators select interventions for addressing alcohol misuse on their campuses. CollegeAIM rates nearly 60 individual- and environmental-level intervention strategies based on factors such as effectiveness in achieving targeted outcomes; estimated cost of adoption, implementation and maintenance; and barriers to implementation. NIAAA will be working with its College President's Working Group to hold a series of regional workshops to introduce CollegeAIM to institutional officials and show them how it can be used on their campuses. NIAAA also is supporting research to evaluate the use of alcohol screening and brief intervention for preventing and reducing alcohol misuse among young adults in clinical and non-clinical settings.

Alcohol use by older adults is emerging as an important area of emphasis for NIAAA. Older adults may be more sensitive to alcohol's effects, more likely to suffer from health problems exacerbated by heavy drinking, and more likely to experience adverse alcohol-medication interactions. Additional research is needed to more fully understand how alcohol differentially affects this population.

Reflecting its increased emphasis on developing new medications to treat AUD, NIAAA established a Division of Medications Development (DMD) to coordinate efforts to identify, screen, and evaluate promising compounds. Through the NIAAA Clinical Investigations Group (NCIG), DMD is conducting "fast success/fast fail" phase II clinical trials of novel and repurposed compounds in collaboration with the pharmaceutical industry. NCIG is currently evaluating gabapentin encarbil, an FDA-approved medication for restless leg syndrome and nerve pain that has shown promise for reducing heavy drinking and promoting abstinence in individuals with AUD. NIAAA is also working to bridge the gap between basic and clinical research through the Small Business Innovation Research and Small Business Technology Transfer programs. Under these programs, NIAAA is funding studies intended to result in the submission of an Investigational New Drug application to FDA for the development of medications to treat AUD or related conditions.

NIAAA continues to support the development of medications for alcoholic liver disease, especially alcoholic hepatitis, a serious and often fatal consequence of alcohol misuse for which there is a dire need for new treatments. Potential therapies for alcoholic hepatitis currently being tested include: probiotics; an interleukin inhibitor, which targets a signaling molecule produced by immune cells; and immunoglobulin, which binds lipopolysaccharides in the gastrointestinal tract. Through NIAAA's intramural research program, scientists are studying the link between endocannabinoids and hepatocellular carcinoma, a serious form of liver cancer with a high mortality rate and no adequate treatment. Their research supports a role for endocannabinoids in tumor promotion and raises the possibility that compounds that block endocannabinoid action could be used to treat this form of cancer. NIAAA intramural investigators have also developed and filed for a patent on compounds that inhibit both peripheral cannabinoid receptors and inducible nitric oxide synthase. These inhibitors show promise for treating liver and lung fibrosis in pre-clinical studies, and NIH's Office of Technology Transfer is currently pursuing licensing of these compounds to the private sector for further development and eventual commercialization.

For individuals undergoing treatment for health conditions associated with excessive alcohol consumption, monitoring their alcohol use is important. NIAAA issued

the “Wearable Alcohol Biosensor Challenge” to stimulate the development of an unobtrusive, real-time, continuous alcohol monitoring system. The biosensor is expected to facilitate alcohol research, enable clinicians to accurately assess their patients’ alcohol intake, and help individuals monitor their own drinking. NIAAA is currently testing eight biosensor prototypes submitted in response to the Challenge.

NIAAA participates with other NIH Institutes, the Department of Defense, the Department of Veterans Affairs, and the Department of Education to accelerate the discovery of underlying mechanisms of post-traumatic stress disorder (PTSD). Approximately one-third of individuals who have had PTSD have had AUD at some point in their lives, and an estimated 30–60 percent of patients seeking treatment for AUD meet criteria for PTSD. Both conditions are linked to dysregulation of brain stress systems, and research suggests that alcohol use may increase PTSD risk by altering the brain’s ability to recover from traumatic experiences. Scientists in NIAAA’s intramural research program are conducting studies to understand how alcohol and stress affect the structure and function of brain circuits critical for the regulation of emotion, cognition, and behavioral control over alcohol and other drug seeking. NIAAA also supports research to develop interventions for preventing and treating co-occurring AUD and PTSD including studies aimed at identifying and overcoming barriers to the diagnosis and treatment of these conditions.

For more than 45 years, NIAAA has supported a diverse portfolio of research and related initiatives aimed at understanding the effects of alcohol on health and wellbeing. Efforts such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative are expected to spur an explosion of new knowledge about brain structure and function and yield unprecedented insight into brain diseases including AUD. To capitalize on these and other opportunities in alcohol research, it is essential to cultivate a talented and diverse research workforce. Therefore, NIAAA will continue to support robust, research training and career development experiences for emerging and established scientists. NIAAA also will pursue efforts to enhance the incorporation of addiction medicine into clinical training, thereby facilitating the translation of alcohol research into practice.

PREPARED STATEMENT OF JON L. 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 2017 budget request for the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH).

INVESTING STRATEGICALLY IN DISCOVERY

NIGMS-funded scientists investigate how living systems work at a range of levels, from molecules and cells to tissues, whole organisms, and populations. NIGMS believes that, as in finance, a diverse research investment is wise because it maximizes the opportunity for breakthroughs. NIGMS supports a diverse population of scientists and a broad portfolio of science at institutions dispersed across the United States.

NIGMS has a longstanding commitment to nurturing creative thought that produces new knowledge. In turn, this knowledge grows into tangible health solutions. Again this year, two long-time NIGMS grantees won Nobel prizes in Chemistry for their groundbreaking work about basic biological processes: in this case, how cells repair damaged DNA. The work, which has led cancer researchers to develop useful drugs, explains how cells respond to DNA injuries from ultraviolet radiation or chemicals like the carcinogens found in cigarette smoke, as well as how cells fix copy errors in the genetic code that accumulate naturally during cell division. Another NIGMS grantee shared the 2015 Albert Lasker Basic Medical Research Award (“the American Nobel”) for his work on the DNA-damage response—a set of actions that cells undergo to protect their genomes against a nearly constant barrage of minor DNA damage. It is clear that seminal discoveries reflecting decades of careful study of fundamental living systems can have very practical outcomes in treating deadly conditions like cancer.

NIGMS values the time-tested practice of supporting investigator-initiated research grants that unleash the creativity and energy of investigators across the country to solve important biomedical problems essential to progress in medicine. Leaving discovery to scientists, NIGMS nonetheless charts its course guided by its strategic plan that commits to public service, careful stewardship of taxpayer funds, and a focus on efficiency and effectiveness.

NIGMS STRATEGIC PRIORITY: SUPPORT INVESTIGATOR-INITIATED BIOMEDICAL RESEARCH

NIH-funded scientists have faced increased competition to obtain grant funding over the past several years. As one step in enhancing the efficiency of this process, NIGMS developed and is currently piloting a new way to fund scientists. The Maximizing Investigators' Research Award (MIRA) program provides support for the NIGMS-relevant research in an investigator's laboratory (via a single, 5-year grant), with the goal of giving investigators greater stability and flexibility and enhancing scientific productivity and the chances for important breakthroughs. The program also aims to help distribute funding more widely among the Nation's highly talented and promising investigators. NIGMS extended its first MIRA funding opportunity to established (experienced) investigators whose grant support would expire this year or next: approximately 25 percent of the eligible pool applied, using a streamlined application that outlined a broad vision for their work and its projected significance. Peer reviewers, the Institute's Advisory Council and NIGMS staff considered a number of criteria when judging MIRA proposals in addition to the applicants' research vision, including their record of scientific productivity and contributions to training the next generation of researchers. The program, which the Institute is also testing with a cohort of junior investigators, has been well-received by the community: "[MIRA] appears to be more 'organic' and 'flexible' than the traditional R01 model, and intuitively seems more compatible with the manner in which ideas, hypotheses, and unexpected discoveries emerge from focused and sustained lines of research," said one MIRA applicant. The Institute is capturing data to evaluate how well program goals are met.

Some areas of biomedical investigation require groups of investigators to work together to ensure synergistic, interdisciplinary expertise and a diversity of thought applied to complex problems. In addition to our programs that support single investigators, NIGMS also funds larger, team-based scientific research. These programs involve multiple investigators and can include facilities or cores, and training and outreach activities. Important areas of team-based research supported by NIGMS are the specialized Centers for HIV/AIDS-related structural biology. These Centers tackle difficult problems such as HIV interactions and viral evolution and mechanism of HIV-virus fusion dynamics with host cells. Their work has laid the foundation for the development of new AIDS drugs and possible vaccines. Other areas of team-based research funded by NIGMS that have had an important scientific impact include the National Centers for Systems Biology. By investing in these centers for over a decade, the program has funded 228 group leaders and directly supported 268 graduate students and 278 postdoctoral fellows; with an impact of approximately 2,000 peer reviewed research papers. As a testament to this program, today many universities have departments and training programs in systems biology, home to researchers whose work is now supported by investigator-initiated R01 grants. Through its strategic plan, the Institute will explore new models for supporting team science that may be more efficient ways to promote important collaborations than are current funding strategies.

NIGMS STRATEGIC PRIORITY: BUILD AND MAINTAIN A DIVERSE RESEARCH WORKFORCE

Science has changed dramatically over the past three decades, and the amount of information available about biological systems has grown exponentially. New methods allow researchers to illuminate and investigate the inner workings of cells with unprecedented resolution (see, for example, the discussion below of cryo-EM technology), and to generate expansive datasets that monitor and measure hundreds to thousands of molecular entities in a system, in both time and space. Biomedical research is becoming increasingly interdisciplinary and collaborative, whilst the questions become ever more complex. NIGMS is working to catalyze modernization of the education and training of the next generation of biomedical researchers to meet the rapidly evolving challenges and opportunities of science and medicine. The Institute recognizes that teaching and learning are not one-size-fits-all endeavors, and that institutional context matters. To promote the necessary shifts, NIGMS is helping colleges and universities test new, innovative educational models that develop the skills required for students to become outstanding scientists who conduct rigorous and reproducible biomedical research. New training paradigms will also emphasize the essential role of mentoring in career development. The Institute hopes to promote a culture in the academic community that continually optimizes training strategies to meet the changing needs of the scientific enterprise. Toward achieving these goals, in April 2016, NIGMS is hosting a symposium on the NIH campus to convene stakeholders from the biomedical graduate education community to continue momentum for positive change and showcase innovative approaches in Ph.D. training.

One key element of research excellence is scientific workforce diversity, because capitalizing on the full spectrum of skills, talents, and experiences is essential for solving complex human health challenges. Over the past several decades, the biomedical workforce has benefited from various NIH programs aimed at enhancing diversity. NIGMS, in particular, has demonstrated a strong commitment to training underrepresented individuals through programs supporting all stages of the career development pathway. The Institute has identified a pressing need to focus on career inflection points, notably the transition from trainee to career independence. The Institutional Research and Academic Career Development Award (IRACDA) program addresses this need by combining a traditional mentored postdoctoral research experience with an opportunity to develop academic skills, including teaching, through workshops and mentored teaching assignments at a partner (typically underserved) undergraduate institution. NIGMS recently began an analysis of how well this program is achieving its goals, and the initial results are very good. IRACDA has sponsored about 400 scholars who have completed training since the program's 1999 inception. A substantial number of these alumni (70 percent) hold academic positions at a variety of educational institutions: 35 percent of academic alumni are located at research-intensive institutions; 14 percent work at partner institutions; and the remainder are employed at other institution types. A particularly promising finding is that IRACDA scholars are considerably more diverse than either a comparable pool of NIH-funded postdoctoral fellows or the overall NIH-funded research workforce.

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

In addition to the creativity of the human mind, cutting-edge technology is a catalyst for innovation. However, technology resources are often not accessible to investigators because of limited supply, location, or cost. NIGMS is using a range of approaches to improve the Nation's research infrastructure, providing investigators better access to critical, shared research resources and technologies. For the past few decades, X-ray crystallography has been the method of choice to allow researchers to take three-dimensional "pictures" of proteins and other molecules important for health and disease. But recently, advances in another technique, cryo-electron microscopy, or cryo-EM, have moved it to the forefront of research into the structures of biological molecules. Unfortunately, despite cryo-EM's advantages over X-ray crystallography and its great promise for helping scientists understanding cell function and dysfunction, state-of-the-art cryo-EM equipment is out of the reach of most of the country's researchers because of its very high cost. To begin to address this problem, NIGMS has started a program to support the purchase and maintenance of cryo-EM technology by regional consortia, giving multiple research groups and institutions access to the equipment. NIGMS hopes to expand this consortia model into larger, regional facilities that will produce significant economies of scale and expand greatly the number of scientists who can use important, cutting-edge technologies.

Through its Institutional Development Award (IDeA) program, NIGMS provides targeted support to increase research capacity in States that historically have had little NIH funding. The IDeA program investment is catalytic and has been successfully leveraged into additional investigator-initiated grants to researchers in IDeA States. For the 8-year period spanning fiscal year 2007 to fiscal year 2014, this additional funding support was \$12 billion, almost a seven-fold return on investment, according to a recent NIGMS program analysis. The IDeA Centers of Biomedical Research Excellence (COBRE) program supports thematic, multidisciplinary centers that expand and develop biomedical faculty research capability and enhance research infrastructure, in part through development of core facilities needed to carry out modern multidisciplinary collaborative research. While the number of COBRE-supported scientists increased only 9 percent between fiscal year 2007 and fiscal year 2014, the productivity of those investigators in terms of scientific publications increased much more—an impressive 43 percent—suggesting that resources are integral to priming the biomedical capabilities of recipient institutions. NIGMS is also supporting the development of clinical research capacity in IDeA States through IDeA Infrastructure for Clinical and Translational Research awards and through joint management, along with the Eunice Kennedy Shriver National Institute of Child Health and Human Development, of the new IDeA States Pediatric Clinical Trials Networks.

While the number of scientific publications per scientist is one metric of success, others include patents and generating interest in commercialization. The Lexington, Kentucky COBRE, for example, has launched two start-up companies to further develop potential cancer treatments identified through NIGMS-funded research. One

is pursuing drug development of a substance that targets molecules that are overactive in certain colorectal and liver cancers.

In this statement, I have shared just a few examples of the remarkable types of returns received from NIGMS' investment in fundamental biomedical research. NIGMS looks forward to the many more advances that will emerge from laboratories across the Nation.

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 2017 budget request for the National Institute on Minority Health and Health Disparities (NIMHD) of the National Institutes of Health (NIH).

ADVANCING HEALTH DISPARITIES RESEARCH

Medical and technological advances have afforded individuals with the potential for longer and healthier lives. However disparities between racial and ethnic minorities, rural, and disadvantaged socioeconomic populations continue to persist. NIMHD leads scientific research that advances understanding of minority health and health disparities. Understanding the complexity of health disparities requires examining how health determinants, biological, social, individual behavior, health system, and environmental factors interact with race/ethnicity and socioeconomic status (SES) to influence health outcomes. For example, studies have shown racial and socioeconomic disparities in pain management, with African American and low SES patients less likely to receive first-line care. NIMHD currently supports a project that examines the use of computer-simulated patients and environments to assess, understand and alleviate pain treatment disparities that are associated with clinician bias. Findings from the study indicate that the utilization of virtual patients allows for greater exposure to racially and socioeconomically diverse patients than what can be found in traditional training settings. As a result, a significant decrease was found in decisionmaking bias for how best to care for the virtual patient.

As the primary Federal agency for guiding and coordinating research to improve minority health and reduce health disparities, NIMHD has taken significant steps in setting a transformational agenda for the field. Recognizing the many factors that drive health disparities and overall health outcomes in minority health, NIMHD is completing a scientific visioning process that will establish a standard social-ecological-biological framework to advance the science of minority health and health disparities.

COLLABORATIVE RESEARCH

A cornerstone of NIMHD's mission is to foster innovative collaborations and partnerships. In order to effectively address health disparities, a multidisciplinary approach involving community, academia, clinicians, service providers, and Federal partners is necessary. NIMHD has a long standing history of fostering partnerships both within and outside of NIH. For example, NIMHD supported Georgetown University, Howard University, and MedStar in their goal to eliminate breast cancer and stroke disparities by transferring knowledge from research to practice within a community setting. Advances of this collaborative effort have led to a community scholars curriculum designed to provide education in research engagement and capacity for community partner organizations to develop and maintain their own research and data systems infrastructure. This partnership also has strengthened the research workforce by developing a fellows program that trains, funds, and mentors students and early stage investigators who are pursuing careers in minority health and health disparities research. More recently, NIMHD in collaboration with the U.S. Environmental Protection Agency, National Institute of Environmental Health Sciences, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, supported the establishment of an indigenous environmental health research center aimed at providing the Hopi and Navajo communities with the ability to conduct their own environmental exposure research. A unique approach to the study is the emphasis on identifying culturally appropriate research methods to be carried out by a multidisciplinary team involving American Indian researchers.

An ultimate example of collaboration is the launch of the Precision Medicine Initiative (PMI). PMI has afforded NIH with the opportunity to form a strong network among several of its Institutes and Centers. NIMHD plays a leadership role in the

efforts to ensure that the establishment of the Precision Medicine Cohort includes standard measures of social determinants of health at baseline and exhibits the diversity necessary for the outcomes of the study to pertain to all Americans. Community engagement is vital to the inclusion of all health disparities populations and therefore, NIMHD has engaged researchers to conduct studies aimed at identifying biomarkers for disease progression (e.g., prostate cancer in African Americans) and drug response in diverse populations (e.g., asthma treatment in Latinos of different national origin) and to examine facilitators and barriers to implementing precision medicine findings in disadvantaged populations. In addition, NIMHD has been at the forefront of ensuring that community organizations are well-informed about the promises of precision medicine. Participation in three White House briefings, meetings and workshops with community organizations, and presentations at national scientific meetings are examples of NIMHD's commitment to engaging all communities in the Precision Medicine efforts.

ENHANCING DIVERSITY OF THE WORKFORCE

NIMHD recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical, and social sciences research workforce. NIMHD expects that efforts to diversify the workforce will lead to the recruitment of the most talented researchers from all groups into research areas relevant to the mission of NIMHD; improve the quality of the educational and training environment; balance and broaden the perspective in setting research priorities; improve the ability to recruit participants from diverse backgrounds into clinical research protocols; and improve the Nation's capacity to address and reduce health disparities.

As the U.S. population becomes increasingly diverse, reflection of that diversity among the biomedical research workforce is vital to the NIMHD research mission. To develop, maintain, and renew our scientific talent pool, it is imperative that we create a climate of opportunity to attract and retain the most talented individuals who can capitalize on innovation and advance scientific discovery. Research has demonstrated that a diversity of perspectives leads to better solutions to complex challenges, including healthcare research and education. NIMHD's commitment to enhancing the biomedical research workforce is evident in our continued support of the Loan Repayment Program, an annual Health Disparities course targeting early career investigators, Clinical Research Education and Career Development Awards, Research Centers in Minority Institutions, and our partnership in the NIH Medical Research Scholars Program. NIMHD's role in all of these programs has produced marked increase in the number of diverse scientists entering and persisting within the research arena.

CONCLUSION

Despite medical and scientific advances there continues to be a disproportionate burden of illness and disease among racial and ethnic minorities and other health disparities populations. Ameliorating these disparities in health outcomes is central to NIMHD's mission. NIMHD envisions an America in which all populations will have an equal opportunity to live long, healthy, and productive lives. Therefore, NIMHD remains committed to scientific leadership in coordinating and supporting highly meritorious research on minority health and health disparities with the goal of improving public health and promoting healthier lives.

PREPARED STATEMENT OF RODERIC I. PETTIGREW, PH.D, M.D., 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 2017 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 healthcare problems. The scope of NIBIB-supported research is vast, from innovations to address paralysis to novel ways to deliver vaccines.

NIBIB is a leader in bringing together many disciplines to solve great biomedical challenges, with a mission that spans all diseases. To achieve that mission, NIBIB supports researchers from every field of medicine and gathers teams of scientists and engineers from diverse backgrounds. These researchers work to develop innovative approaches to advance scientific discovery and address real-world health issues

through new knowledge and new technologies. I am pleased to share a few highlights from the breadth of NIBIB-funded research efforts that are working toward our shared goal of improving public health.

DELIVERING A VACCINE WITHOUT A NEEDLE OR NEED FOR REFRIGERATION

NIBIB's Quantum Grants Program is designed to have a profound, or quantum, impact on a particular healthcare problem. In keeping with NIBIB's mission, projects in this program take an approach that is highly collaborative and interdisciplinary with a focused goal that is achieved through technological innovation. In one Quantum Grant example, researchers have developed a microneedle patch to deliver vaccines without the traditional "shot in the arm." This technology could lead to self-administered vaccines with an easy-to-use, more widely available device that is about the size of a quarter.

The first targeted application is flu vaccination. Influenza is a major cause of illness and death worldwide. While vaccines are effective in preventing infection, access in rural and medically underserved areas is a challenge. A new microneedle patch addresses these challenges in that it can be self-administered, does not require refrigeration, and could be delivered in the mail. The single-use patch is also painless and research has indicated that all of these benefits could lead to higher rates of immunization and reduce flu-related deaths and hospitalizations.

A clinical trial is underway to assess the use of microneedle patches in vaccinating against influenza. The patches contain very thin and short microneedles, which are barely visible to the eye. As the patch is applied to the skin, these microneedles painlessly penetrate the upper layers of the skin and deliver the vaccine. The study includes 100 healthy adults and seeks to assess the safety of the microneedle patch, how the body's immune system responds to the vaccine delivered through the patch, and participants' opinions about using the patch. Initial results indicate that influenza vaccination using the microneedle patch generates immune responses at least as good as conventional injection, that the microneedle patch has a very good safety profile, and that study participants strongly prefer vaccination by the microneedle patch over a traditional flu shot.

USING IMAGING TECHNOLOGY TO BOTH DIAGNOSE AND TREAT DISEASE

For decades, imaging technologies such as magnetic resonance imaging (MRI), ultrasound, and computed tomography (CT) have provided a window for a non-invasive look inside the body to locate and assess tumors or damaged tissue. Increasingly, research in imaging technology is not only discovering improved ways to see inside the body but also developing highly integrated systems to provide rapid feedback to guide treatment.

In another Quantum Grant Program example, researchers are using an improved imaging technology that combines diagnosis and an intervention for acute ischemic stroke. Strokes are a major cause of death and neurological injury. Acute onset of stroke-like symptoms is a medical emergency and rapid diagnosis and treatment are critical to saving as many brain cells as possible. This novel method is estimated to save from one to two hours per patient, and therefore save considerable brain tissue.

Currently, stroke diagnosis and monitoring is performed with imaging in dedicated CT or MRI imaging suites separate from where stroke is treated, requiring the patient to be moved and costing precious time while brain tissue is damaged through loss of blood supply. The treatment of stroke caused by blocked blood vessels involves specialized catheter-based angiography to restore blood supply to the affected brain area. The breakthrough of this Quantum Grant award is the integration of angiography with advanced imaging capabilities into a time-saving and cost-efficient platform that is housed on a single machine. This is possible through a revolutionary image acquisition and reconstruction technique that fundamentally challenges the traditional methods now in use. For the first time, this new technique produces rapid, high resolution CT images and enables immediate treatment of strokes caused by blood vessel occlusion (blockage).

Advances to current imaging technologies such as this could lead to more rapid and personalized treatment of occlusion stroke, potentially resulting in better neurological outcomes for patients.

FINDING RARE CELLS AMONG BILLIONS FOR EARLY DETECTION OF CANCER

Cancer tumors shed tiny fragments that can enter the blood stream. Capturing these obscure traces of cancer allows them to be analyzed so that treatment can be designed specifically for each patient. Similarly, the technology can be used to monitor treatments for effectiveness. This individualized approach, which identifies and

targets the specific genetic features in each person, is the hallmark of the President's Precision Medicine Initiative.

In an initial phase of an ongoing NIBIB Quantum Grant Program, researchers developed the iChip, a microfluidic device that can capture one circulating tumor cell (CTC) among one billion red blood cells. This means that in a small vial of blood there could be from 1—100 CTCs among 80 billion red-blood cells. In one study, human cancer cells were captured using this technology and analyzed, then tested in animal models to see which treatment was most effective. Researchers are also working to make the device so small that it can be used at the point-of-care to deliver results rapidly. This real-time measurement of CTC numbers could one day allow doctors to promptly change or stop ineffective treatments, such as when cancer cells become resistant to a particular chemotherapy drug.

The technology has also been developed to isolate clusters of CTCs. Clusters are even rarer than single CTCs, but are 50 times more potent in producing metastatic spread of cancer. Identifying and capturing CTC clusters could help identify and study more aggressive cancers.

Building on this research, the investigators are now turning toward a new phase of development that can capture pieces of DNA shed from cancer tumors. Researchers are looking at this new use of the technology as a sensitive method for early identification of prostate and lung cancer. In both types of cancer, detection is challenging and cancers are often discovered when tumors are of a significant size, or the cancer has spread. This technology also has the potential for non-invasive monitoring to determine if the selected treatment is working. The new approach integrates the CTC iCHIP technology with known methods to identify genetic markers for early detection.

USING NEURAL STIMULATION TO ADDRESS PARALYSIS

Each year 12,500 new cases of severe spinal cord injury (SCI) occur (2015, National SCI Statistical Center). Currently, the approach for treating this type of injury is to provide rehabilitation therapy to limit further damage. In these patients, the pathways that send information about sensation from the legs to the brain and from the brain to the legs to control movement are disrupted. For years physicians thought that recovery of function in spinal cord injury was not possible.

Now, after years of basic research and recent developments in a very small number of patients, investigators are working to understand how neurostimulation of the spinal cord might help patients regain function. Recent studies have shown that it might be possible to reawaken the neural pathways along the spinal cord after injury. A small number of patients have received electrical stimulation either implanted under the skin next to the spine (epidural) or placed on top of the skin along the spine (transcutaneous) and have regained the ability for some limb movement and the ability to stand unassisted for a brief period of time. Patients receiving stimulation also report that they have regained other functions important for improved quality of life, such as control of blood pressure, temperature, bladder, bowel, and sexual function. Further study is aimed at understanding how electrical stimulation can most effectively lead to restored function and how stimulation can be customized to work best for individual patients.

NIBIB is also part of the President's BRAIN Initiative and part of this effort is to develop tools and technologies that lead to a better understanding of brain function. Many of the technologies developed for understanding the brain can be used to understand the spinal cord and the peripheral nervous system. Understanding these systems will help us know how to help people overcome these devastating injuries.

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 and this integration of disciplines is what defines NIBIB's approach. NIBIB is committed to supporting such convergent teams of researchers to solve major biomedical challenges that will improve the health of all Americans.

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 2017 budget request for the National Institute of Diabetes and Di-

gestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). NIDDK supports research on many chronic, consequential, and costly diseases and conditions that affect millions of Americans. These include diabetes and other endocrine and metabolic diseases; digestive and liver diseases; kidney and urologic diseases; blood diseases; obesity; and nutrition disorders.

DISCOVERY RESEARCH

NIDDK-supported scientific research is expanding knowledge of human health and disease. Testing novel approaches and hypotheses has led to new discoveries that continue to build foundations for innovative strategies to improve health and quality of life. These advances include researchers revealing a critical role for immune cells in the development and activity of calorie-burning beige fat, a finding which could provide new therapeutic targets to treat obesity and metabolic diseases. Genetic research examining data from hundreds of thousands of people has more than doubled the number of genetic regions known to be associated with obesity and body fat distribution patterns. Additionally, studies have found that a virus in the intestinal tract could have beneficial effects similar to those granted by gut bacteria, and research in humans and in mice has shed new light on how genetic factors shape the composition of the gut microbial community and affect metabolism. New discoveries could also yield novel, non-antibiotic approaches to treat or prevent urinary tract infections (UTIs). One group of scientists discovered a new mechanism by which bacteria such as *E. coli* survive and promote UTIs, and another found that in mice, bacteria that do not cause symptomatic UTIs may be an effective therapy against ones that do. These and other discovery-based investigations continue to seek fundamental knowledge about living systems that can form the basis for new strategies to protect and improve health.

In fiscal year 2017, NIDDK will continue to support pioneering discovery-based research, including efforts to build integrated human pancreatic islet and liver tissue chips that can be used to study metabolism and model human diseases such as diabetes. NIDDK also will support research to define interactions between the host and the gut microbiota that can regulate both healthy and disease-related physiological processes. These projects aim to discover specific human gut microbiota-derived factors that affect or are affected by the human host's own physiology and disease and then investigate how these factors affect the gut and other organs. Harnessing knowledge of normal kidney development, the NIDDK-funded (Re) Building A Kidney consortium continues to forge new approaches to treat kidney injury and disease by enhancing kidney repair and promoting the generation of new kidney cells. Additionally, the Human Heredity and Health in Africa (H3Africa) Initiative will continue to support a network of African investigators to study the interplay between environmental and genetic factors affecting

the health of African populations. To accomplish this, the H3Africa Initiative aims to enhance infrastructure and support collaborations to enable African researchers to carry out large-scale studies on African populations.

CLINICAL RESEARCH

Clinical studies are integral to research on the broad spectrum of diseases for which NIDDK has research responsibility. Through innovative design and rigorous testing of interventions, NIDDK-supported researchers are improving lives with new approaches to prevent, treat, and reverse diseases and disorders. For example, researchers have developed a potential new method to use examination of the eye to diagnose diabetes-related nerve complications, a strategy that could replace the use of skin biopsies to diagnose these problems. A new research model of the human small intestine was developed by growing intestinal tissue from human stem cells, resulting in tissue that can perform digestive functions and be transplanted into mice. This advance expands scientists' ability to study the intestine under conditions similar to those in the human body. Researchers found that a process called "desensitization" can alter the immune system of a person with kidney failure so that their body can accept a kidney transplant from an incompatible live donor, rather than waiting for a more compatible cadaveric donor or remaining on dialysis. Another group found that people who choose to donate one of their kidneys to someone with kidney failure remain relatively healthy 3 years after their donation, suggesting that living donor kidney donation can improve the health of donor recipients without compromising the health of the donor, at least within the first 3 years after donation. Genetic studies also found six new genetic regions associated with risk of developing both inflammatory bowel disease and immunoglobulin A nephropathy, a major cause of kidney failure worldwide. These findings may lead to better understanding of the causes of both diseases and, eventually, to new treatments.

NIDDK-supported clinical research will continue to pursue improved treatments for diseases and conditions relevant to the Institute's mission. The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) is a major trial that recently began to compare commonly used diabetes medications, with the goal of determining which drug—in combination with metformin—is most safe and effective for patients. NIDDK will also continue its participation in the Accelerating Medicines Partnership (AMP) Type 2 Diabetes Project—a public-private partnership between NIH, the Food and Drug Administration, biopharmaceutical companies, and non-profit organizations—that seeks to identify and validate the most promising biological targets for diagnostic and drug development. AMP has developed and is expanding a Knowledge Portal that consolidates results from 28 large human genetic studies of type 2 diabetes and supports analyses that can shed light on possible drug targets. The Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study—conducted in collaboration with the Crohn's and Colitis Foundation of America's Pediatric Research Organization for Kids with Intestinal Inflammatory Diseases (PRO-KIIDS) Network—will continue its efforts to provide a better understanding of how children newly diagnosed with ulcerative colitis (UC) respond to corticosteroids, the standard initial therapies used to treat this disorder. The PROTECT study results could help predict how children with UC will respond to treatment and thus lead to more personalized therapies and improved outcomes. Also, NIDDK-sponsored Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network continues to conduct innovative, collaborative studies of interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The MAPP Research Network's work can pave the way to better understanding of what causes these conditions, improved diagnosis, ways to prevent onset, and more effective treatments. The Network is also studying the possible relationships between urologic pelvic pain and other chronic pain disorders, such as irritable bowel syndrome and fibromyalgia.

New clinical research initiatives include the launch of the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer. This consortium (co-funded by NCI) will study chronic pancreatitis (CP) and factors that link CP to other diseases. The consortium will conduct studies to improve understanding of CP's disease processes and how these processes are related to outcomes such as diabetes and development of pancreatic cancer. NIDDK will also support clinical research into how normal or altered sleep and circadian rhythms affect metabolism and disease outcomes such as diabetes. Additionally, through NIH's Common Fund, the ICD-Pieces trial will test whether a collaborative model of primary and subspecialty care enhanced by a novel health information technology platform could result in better care and quality of life for those with multiple conditions, such as chronic kidney disease, diabetes, and hypertension.

SUSTAINING THE BIOMEDICAL WORKFORCE

The future of biomedical research and the continued improvement of the Nation's health depend critically on maintaining a strong and vital work force. NIDDK strives to ensure that new investigators can realize their potential for contributing to biomedical research, and that today's generation of young scientists will view research as a viable career. To this end, NIDDK offers a comprehensive set of programs that support investigators from their initial training as medical and graduate students through their evolution into established scientists. In addition to providing institutional and individual grants to support graduate and post-graduate trainees and physician-scientists, NIDDK supports one of the largest career development programs at NIH. It complements this program with a biennial workshop that provides knowledge and skills necessary to transition to independent research careers, including career advice and information about the NIDDK's grant review process. NIDDK also offers career development awardees a small supplemental grant program to help establish an independent research program. Early stage independent investigators (ESIs) are generously supported with priority funding. Recognizing that the first renewal of an ESI's first grant is typically the final barrier to becoming an established investigator, NIDDK has targeted ESIs with a workshop that provides additional guidance, and it has instituted a pilot program that offers them priority funding when they renew.

To build and sustain a diverse research pipeline, NIDDK has several programs aimed at facilitating research by and mentorship of underrepresented groups at various career stages. The Short-Term Research Experience for Underrepresented Persons (STEP-UP) program provides hands-on summer research experience for high school and undergraduate students interested in exploring research careers. NIDDK's Network of Minority Health Research Investigators fosters mentoring rela-

tionships between senior and early-career scientists, and NIDDK-supported awards enable mid-career health professionals to conduct research while acting as mentors to early-stage investigators from diverse backgrounds underrepresented in biomedical and behavioral research.

In closing, NIDDK is committed to a vigorous, multi-pronged research portfolio including both discovery-based and clinical research. Five principles continue to guide NIDDK's future research investments: 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.

PREPARED STATEMENT OF PAUL SIEVING, M.D., PH.D., DIRECTOR, NATIONAL EYE INSTITUTE

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2017 budget request for the National Eye Institute (NEI) of the National Institutes of Health. Vision science is at the leading edge of neuro-regenerative medicine and discovery science in brain connectivity. I want to share our latest progress and goals in neuroscience, regenerative medicine, gene discovery, and gene therapy.

NEI AUDACIOUS GOALS INITIATIVE

The NEI Audacious Goals Initiative (AGI) is a bold, strategic investment in neuro-regenerative medicine that will enable the restoration of vision through regeneration of the retina—the light-sensitive tissue in the back of the eye. AGI focuses on photoreceptor neurons and retinal ganglion cells. Photoreceptors capture the light necessary for initiating vision, while retinal ganglion cells transmit these light-induced signals to the brain and can degenerate in glaucoma and other optic nerve diseases. Vision scientists have taken the first steps toward achieving the regeneration of these cells by converting stem cells into mature retinal cell types and are integrating these cells into existing retinal circuits. In order for these regenerated neurons to send signals to the brain, they need to grow long connections, called axons, and correctly wire themselves to the appropriate partners in the retina and the brain—a goal that will require new tools and a better understanding of the underlying biological processes.

Last year, NEI awarded the first five AGI projects to develop functional and metabolic imaging technologies that are capable of visualizing a single live cell. For example, adaptive optics (AO) technology has been developed to successfully image a single photoreceptor in patients and track that particular cell in subsequent patient visits. This powerful tool allows clinicians to non-invasively monitor the degeneration of the cell and conversely to image its replacement by healthy stem cells. Prior to this technology, imaging was severely limited by distortions that bent light waves irregularly. In addition to AO, advanced magnetic resonance imaging technology is being developed to assess regeneration of damage to the optic nerve. These five imaging teams were brought together in a collaborative consortium to share data, technology, and early results in order to speed progress toward scientific goals. This consortium also facilitates input and guidance by NEI program staff as well as by an external scientific oversight committee. Importantly, the AGI is a participatory scientific endeavor that actively gathers input from the vision community and the broader neuroscience community in the form of expert workshops and town hall meetings.

NEI is currently reviewing applications from a second AGI funding opportunity to screen cellular and molecular entities critical to the regeneration of neurons, guiding their axons to targets, and making new functional connections. NEI anticipates that once the unknown factors (genes, proteins, signaling molecules, etc.) involved in regenerating retinal ganglion cells and photoreceptors are discovered, the work will advance to specific projects to understand the biological mechanisms through which these factors influence regeneration.

It is noteworthy that AGI has catalyzed the field of neuro-regenerative medicine, with over 20 investigator-initiated projects awarded by NEI in fiscal year 2015. While AGI is independent of the President's BRAIN Initiative, many vision scientists are BRAIN grantees, and BRAIN research will accelerate AGI efforts to regrow and regulate retinal neurons and their connections in the eye and brain.

Proliferative diabetic retinopathy (PDR) is a serious complication of diabetes, in which vascular endothelial growth factor (VEGF) secreted by the retina triggers the proliferation of abnormal leaky blood vessels. Accompanying vitreous hemorrhage and retinal detachment can lead to permanent vision loss. Since the 1970s, doctors have treated PDR with a laser therapy, but this treatment can damage night and side vision, so researchers have sought improved therapies. Lucentis is one of several drugs that block VEGF and has been shown to be effective in other eye diseases. Diabetic Retinopathy Clinical Research Network (DRCR.net) has 400 retina specialists in over 41 States, one third are university based, and the rest are from community-based practices. A DRCR.net trial found that Lucentis is highly effective in treating PDR, reversing some vision loss without affecting side vision. By comparison, laser treatment merely preserves existing central vision but does not reverse losses. The new research findings demonstrate the first major therapy advance for PDR in nearly 40 years. The network also conducted a study of three anti-VEGF drugs for diabetic macular edema: Lucentis, Eylea and Avastin. After 2 years, patients with mild vision loss at baseline had similar improvements in visual acuity from all three drugs. However, patients with moderate to severe vision loss at the start of the trial had slightly better improvement with Eylea and Lucentis than the less costly drug, Avastin. From these results, patients and doctors can weigh baseline vision, expected clinical outcomes, and costs when choosing a personalized treatment strategy.

For patients who live in rural or urban underserved communities, telemedicine can be used to remotely screen, monitor and diagnose disease. DRCR.net just launched a new protocol to explore whether telemedicine using a new ultra-wide field imaging technology can allow specialists to remotely identify DR in a patient and to determine what follow up care is indicated. NEI also has supported telemedicine technology development through its Small Business Innovation Research program, e.g., automated retinal scanning technology to detect DR and monitor images at remote clinical sites.

Using patient-specific induced pluripotent stem cells (iPSCs), NEI researchers are developing the first personalized therapy for the “dry” form of AMD. The retinal pigment epithelium (RPE) is a single layer of cells that carry out the critical function of nourishing and supporting the adjacent photoreceptor cells. In dry AMD, RPE cells start to die, leading to photoreceptor cell loss and visual impairment. The NEI intramural research team has developed a clinical-grade manufacturing process to derive iPSCs from AMD patients and convert them into RPE tissue. The RPE tissue is delivered using a biodegradable scaffold that helps integrate and maintain proper orientation of the tissue in the back of the eye. The entire RPE tissue manufacturing process takes only 142 days after a blood draw from an AMD patient. Patient-derived tissue has the distinct advantage over donor tissue as it is less likely to be rejected by the immune system. In preclinical work to prepare for a human trial, the NEI team demonstrated that transplanted tissue integrates in the retina and restores lost function in a pig model of retinal degeneration. Success in the pig model, along with production of clinical grade iPSC has paved the way toward filing an application for Investigational New Drug (IND) with FDA in 2017.

iPSC technology is a potentially powerful research tool that enables scientists to transfer their knowledge of known disease pathways in particular cells and organs to shed light on the impact of these same disease mutations in entirely different cell types of other organs. For example, iPSCs derived from a heart disease patient have a mutation in the gene STAT3. This mutation impairs blood vessel growth, and immune and wound-healing responses. The STAT3 gene has also been suggested to play a role in RPE immune responses and in molecular signaling that may lead to AMD-like symptoms in patients. The NEI team is now testing RPE tissue derived from this patient’s cells to understand the role of STAT3 in AMD.

Cataracts are a clouding of the lens caused by misfolding and aggregation of lens crystallin proteins, and can result from many causes including side-effects of drugs like steroids, or surgery, or most commonly from aging. Cataracts occur in over half the population over age 70 and are a major cause of vision loss in older adults. Researchers identified a class of molecules that bind to crystallins, reverse their aggregation and restore lens transparency in mouse models of cataract. These agents could be delivered via eye drops, potentially eliminating the need for costly surgical cataract removal.

GENETICS AND GENE THERAPY

In the largest-ever Genome Wide Association Study (GWAS) for AMD, NEI investigators were part of an international team that studied more than 12 million gene

variants from more than 43,000 participants with and without AMD. The group identified 52 associated common and rare gene variants associated with AMD. The success of this study, particularly for rare variants, was predicated on the extremely large sample size of participants and bringing together an interdisciplinary team of clinicians, geneticists, and bioinformatics experts to analyze “big data.”

Glaucoma is the second leading cause of blindness globally. It is a group of conditions that damage the optic nerve and have a genetic predisposition. A consortium called the NEI Glaucoma Human Genetics Collaboration Heritable Overall Operation Database (NEIGHBORHOOD) recently identified three new genes that contribute to the most common form of glaucoma, increasing the total number of such genes to 15. One new gene is an enzyme that protects cells from oxidative stress. Another gene had previously been implicated in a rare form of severe early onset glaucoma. Despite the high heritability of glaucoma, identifying glaucoma genes has been a challenge and the biological mechanisms are poorly understood. To address the mechanistic challenge, NEIGHBORHOOD researchers integrated eight independent GWAS, involving over 37,000 glaucoma patients and controls to better understand genes and phenotypes.

A pioneering technology called optogenetics introduces light-sensing proteins into cells that are not otherwise light sensitive. In retinitis pigmentosa (RP), the light-sensitive photoreceptor neurons have died, however many other neurons in the retina are preserved. NEI investigators have established proof-of-principle with optogenetics gene therapy in blind mice. By delivering light-sensing proteins directly to retinal bipolar cells, they effectively bypass the dead photoreceptor neurons upstream and can elicit a visual response. This exciting work is being translated into a clinical trial. There are many gene mutations that cause RP, yet optogenetics is not treating a single mutation; a single therapy that restores visual responses could have widespread application.

A major scientific breakthrough in the past few years was the development of a gene editing tool called CRISPR/Cas9, in which specific DNA mutations can be changed in specific cells. As a research tool, this system allows researchers to introduce molecular changes in cell cultures or animal models to study the function of individual proteins. The tool also has fundamentally important implications for clinical therapy in adult tissues. NEI is funding research that is correcting genetic mutations in stem cells created from patients with genetic mutations for RP, Usher syndrome, and Best disease. In the future, these corrected stem cells could be used as a cell therapy. NEI also is funding research using CRISPR/Cas9 for a wide variety of other ocular disorders affected by specific gene mutations such as a form of glaucoma and Fuchs’ corneal dystrophy.

RETINA ORGANOID CHALLENGE COMPETITION

NEI is preparing to launch a \$1.5 million challenge competition to catalyze therapies for retinal diseases by developing retina organoids. Organoids are 3D, self-assembling, mini-organs grown in a dish from human stem cells. They can be used for disease modeling, drug development, and therapeutic transplantation. On April 4, 2016, NEI held a technical planning meeting of industry and academic experts to review progress in organoid engineering of the retina and other organs, and to help design challenge parameters. The Congress requested a retina disease challenge in NEI’s fiscal year 2016 Appropriations Report. This competition dovetails with the AGI and will accelerate retinal therapies since the human tissue-based models will aid in developing and testing regenerative therapies for retinal neurons.

FUTURE DIRECTIONS

The audacious goal to regrow new neurons in the retina and restore vision builds on a foundation of audacious science that is described here. In the near terms, we will advance the understanding of mechanisms that underlie eye disease. The mechanistic knowledge will propel the drive for clinical applications that help fulfill the promise of gene and cell therapies that benefit patients.

PREPARED STATEMENT OF MARTHA J. SOMERMAN, D.D.S., PH.D., 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 2017 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. In keeping

with this mission, NIDCR's research spans multiple disciplines, scientific approaches, and research directions. Today, I will highlight selected areas of NIDCR-supported research that hold particular promise to improve oral health. These include efforts to understand the role of the oral microbiome, develop innovative tools and technologies, address emerging public health challenges, and strategies to cultivate and sustain future oral health researchers.

FOUNDATIONAL DISCOVERIES

The community of bacteria and other microbes that live in our mouths (the oral microbiome) not only has the potential to cause disease, but also plays a critical role in maintaining our health. Although we have learned much about the oral microbiome, one of the most important unexplored questions is how health-promoting and disease-causing bacterial communities are acquired at birth and how the balance between the two is developed and maintained over time. To answer this question, NIDCR-supported researchers are studying the oral microbiomes of children from birth to adolescence to determine what happens to bacterial communities during different stages of childhood. Scientists are using genetic techniques as well as considering specific environmental factors such as the delivery method at birth, the use of antibiotics in the hospital, and whether the infant was fed breast milk or formula. More knowledge about how individuals acquire their own unique oral microbiome could result in new strategies to help keep our mouths and bodies healthy.

We have made tremendous progress in developing new approaches to catalogue the oral microbiome. However, understanding the types of bacteria present isn't enough. We also need to understand how the microbiome community in the mouth is organized and how its complex structure helps to maintain health and contributes to disease. NIDCR-funded scientists have developed a new imaging technique to visualize the multiple layers of bacteria that live on each surface of the oral cavity. They have observed that some microbial communities gather and form distinctive three-dimensional structures on teeth that look like spiny hedgehogs and cauliflowers. These structures create the foundation upon which other bacteria attach and grow and eventually become the plaque that causes dental caries (tooth decay) and periodontal disease (an inflammation of the tissues supporting the teeth). This new imaging technique will also be a valuable tool for researchers exploring potential drug therapies to change the structure of the microbial community and treat oral infections.

INNOVATIVE TOOLS AND TECHNOLOGIES

Early detection and diagnosis of oral cancer is essential for successful treatment. Because most people are not diagnosed until after a tumor has spread to other tissues, the survival rate for people with oral cancer—especially for African American males—is among the lowest for the major cancers. The current procedure for detecting oral cancer starts with inspecting the oral cavity for suspicious lesions. If a suspicious lesion is identified, a sample of the tissue is typically removed (i.e., a biopsy) and sent to a lab to check for cancer cells. To increase the likelihood that oral cancer will be detected earlier and more accurately, NIDCR-supported researchers have developed a handheld microscope to screen for oral cancer in the dental office. Roughly the size of a pen, the microscope uses an innovative technology called 'dual-axis confocal microscopy' to make it easier to discriminate between healthy and potentially cancerous tissue. Using this tool, clinicians will be able to make more informed decisions about whether or not to remove suspicious-looking lesions for analysis—thus reducing the need for unnecessary invasive procedures. This novel technology will help meet a critical need for more effective tools to screen individuals at risk for oral cancer and could also be used to detect the recurrence of cancer following treatment.

Mobile health, or mHealth, is an exciting technology that encourages people to make healthy lifestyle changes. For example, many of us wear wrist bands to count the number of steps we take every day or we use mobile applications to keep records of what we eat and drink. NIDCR-supported researchers are taking a lead in developing mHealth tools to easily and accurately track oral health behaviors, such as tooth brushing. In collaboration with engineers at Oral-B, NIDCR-supported researchers have developed an electronic toothbrush with a built-in sensor that collects precise data about tooth brushing frequency and duration. By collecting real-time data, this mHealth sensor is helping investigators bypass the need for research participants to remember and accurately report their tooth brushing habits. The objective data gained from this innovative device will increase our understanding

about actual tooth brushing behavior and potentially lead to new approaches to increase motivation for improved oral health behavior.

EMERGING PUBLIC HEALTH CONCERNS

After years of declining cigarette sales in the United States, spurred in part by awareness of the adverse health effects of tobacco use, a new form of nicotine delivery has emerged—the electronic cigarette, commonly called the e-cigarette. The use of e-cigarettes is increasing dramatically among young adults. In fact, according to the Centers for Disease Control and Prevention, e-cigarette use by middle and high school students in the United States tripled between 2013 and 2014. However, very little is known about the chemicals in the aerosol mixtures released by e-cigarettes or the impact those chemicals might have on health. NIDCR recently developed an initiative that funded a number of grants to investigate the effects of e-cigarette chemicals on oral health. A broad range of studies are being supported that include human participants, as well as cell and animal model systems. This research will offer valuable insights into the safety of e-cigarettes and how they affect the oral microbiome, the immune system, and the ability of damaged tissues in the oral cavity to heal.

Many people visit their dentist regularly, which puts dental practitioners in a prime position to address public health issues. Currently, one particularly pressing public health concern is prescription opioid abuse. Because dentists prescribe opioids to treat acute dental and oral pain following dental procedures, it is important to understand the opioid prescribing practices of dentists. NIDCR invests in a valuable resource for conducting these types of clinical studies in real world settings, called the National Dental Practice-Based Research Network (NDPBRN). The Network consists of more than 6,000 dental practitioners in the United States who see patients on a regular basis and are interested in conducting research in their practices. Dental practitioners will participate in a study to assess dentists' knowledge of opioids and the decisionmaking processes and behaviors related to opioid prescription. The findings from this NDPBRN study will increase our understanding about how and why opioids are prescribed by dentists in order to develop strategies to help halt opioid abuse in the United States.

RECOGNIZING OUTSTANDING ORAL HEALTH RESEARCHERS

NIDCR is proud to support three scientists who have been recognized for their innovative research. Two of these scientists are recipients of the Presidential Early Career Award for Scientists and Engineers (PECASE), the highest honor bestowed by the Federal Government upon outstanding scientists and engineers beginning their independent careers. The success of NIDCR-funded scientists in receiving this award is a testament to our commitment to support research training and career development. The third scientist is a longtime NIDCR-supported investigator who recently received recognition as part of the NIH Common Fund's Gabriella Miller Kids First Research program. The program is named for a brave girl who raised funds to support research on childhood illnesses before she died of cancer at age ten. This investigator is identifying the genetic basis for orofacial clefting using DNA sequencing to identify common genes in a large cohort of families. These honors recognize exceptional NIDCR researchers who are striving to improve the lives of children like Gabriella Miller and the oral health of all Americans.

PREPARED STATEMENT OF CATHERINE Y. SPONG, M.D., ACTING 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 2017 budget request for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH).

Understanding human development, both normative and atypical, is at the core of NICHD's mission. Unlike many of the other NIH Institutes and Centers (ICs), NICHD takes a lifespan approach to its work, supporting research that ranges from efforts to increase our understanding of basic biological mechanisms to testing health interventions aimed at improving the lives and health of children, women, and families, including those with disabilities.

MINIMIZING DUPLICATION, MAXIMIZING EXPERTISE

In this increasingly complex world, highly specific expertise may be required to ensure that any preventive measures or development and application of therapies will meet the needs of each affected population. Because of the breadth of its mission, NICHD can provide a lifecourse perspective and a depth of expertise to research efforts related to pregnancy, infants, and the typical or atypical development of children through young adulthood. This breadth also means that NICHD works across scientific disciplines and often seeks or is tapped to lead trans-NIH, collaborative efforts that bring together other ICs' and non-NIH scientists' knowledge and skills so that the overall efforts are additive, not duplicative.

Human Placenta Project.—NICHD is leading an initiative known as the Human Placenta Project that will develop technologies to assess, in real time, the structure and function of the human placenta. The least understood human organ, the placenta has substantial implications for the lifelong health of both mother and child, since so many health issues can be traced back to the earliest stages of development. The Project's goals include understanding normal and abnormal placental development, developing biomarkers to predict adverse pregnancy outcomes, examining the effects of environmental factors, and developing interventions to prevent abnormal placental and fetal development. Each year, NICHD brings together a group of broad thinkers that includes subject matter experts in various technologies, placental biologists, and clinicians to generate creative approaches to developing and applying technologies in new, noninvasive ways to understand placental function. The impact of the Human Placenta Project extends beyond enhancing pregnancy to providing additional insights into health and disease. New knowledge will increase our understanding of tumor biology and transplant medicine as the placenta mimics tumor growth and invasion early in gestation and mediates and promotes the health of two genetically distinct entities.

PregSource™.—About 6.5 million pregnancies occur each year in the United States, and yet we have relatively little scientific information about what constitutes a normal pregnancy. In the coming year, NICHD will launch "PregSource™," a longitudinal, crowd-sourced, citizen science approach that will gather information about pregnancy from the experts—pregnant women. Through web-based questionnaires or mobile apps, PregSource™ will expand our knowledge about what women experience physically and emotionally during pregnancy and after giving birth, the effects of pregnancy on women's lives, the special challenges some pregnant women face (such as health issues related to disability or a chronic health condition), and what features are common to many pregnancies. Ultimately, this information will help to fill the large gap in knowledge about medications used by pregnant women and other issues commonly experienced during pregnancy. In return, PregSource™ will provide participants with links to evidence-based information about pregnancy from 20 trusted national partners, including several NIH ICs and professional societies. Approved researchers can view de-identified, amalgamated information that may suggest fruitful research avenues about pregnancy. This innovative approach to gathering information was based on the highly successful DS-Connect®: The Down Syndrome Registry, which was launched by NICHD and its Down Syndrome Consortium partners in 2013. With more than 3,200 registrants across the United States, DS-Connect® has facilitated recruitment into clinical trials on several aspects of Down syndrome.

Birth Defects.—With other NIH ICs and the Common Fund of the NIH Office of the Director, in fiscal year 2017 NICHD will continue to provide leadership for extended basic and translational research efforts related to birth defects. Structural or functional anomalies affect about 3 percent of births and are the leading cause of infant death in the United States. Through intramural and extramural programs, NICHD supports collaborative teams of basic and clinical scientists studying the developmental biology, epidemiology, and genetics of structural birth defects. New fiscal year 2017 initiatives in structural birth defects research will catalyze the development of new research teams and support data analysis that uses and complements the genomic sequencing data developed under the Gabriella Miller Kids First Pediatric Research program, funded by Congress since fiscal year 2014.

Best Pharmaceuticals for Children.—Although progress has been made in recent years, approximately three-quarters of all medicines marketed still do not carry Food and Drug Administration (FDA) approved labeling for use in neonates, infants, children, and adolescents. Although it is widely recognized that children are not small adults, only five of the 80 drugs most frequently used in newborns and infants are labeled for pediatric use. For many drugs, developmental, metabolic, and pharmacokinetics-pharmacodynamic data are needed for their safe and effective use in children, yet sometimes private pharmaceutical companies are reluctant to incur the

expense of gathering these data. In the Best Pharmaceuticals for Children Act of 2002, which was reauthorized in 2007 and 2012, the Congress charged NIH with setting priorities and funding research on pediatric therapeutic needs, tapping NICHD to lead this effort. Through an active trans-NIH Working Group, NICHD has collaborated with other ICs to identify therapeutic gaps in pediatric diseases, disorders, or conditions for which more complete knowledge of drugs and biologics would benefit specific pediatric populations, and develop future clinical trials. Using this approach, and also consulting with pediatric experts from FDA, academia, and industry, NICHD regularly publishes a prioritized list of drugs or indications that require further investigations. Four additional drugs commonly prescribed for children now have pediatric labeling, with others pending approval at FDA. Most recently, NICHD staff met with FDA pediatric leadership in December 2015 to discuss how to further improve the process for getting drugs labeled for pediatric use.

Rehabilitation Research.—Although NIH was already supporting multiple lines of research focused on medical rehabilitation for physical, sensory, and cognitive disability across the lifespan, the establishment of the National Center for Medical Rehabilitation Research (NCMRR) by the Congress in 1990 provided a new focus on the science of medical rehabilitation and how results could be used to meet the challenges facing individuals with physical disabilities. A component of NICHD, NCMRR leadership emphasizes the need for medical rehabilitation across the lifespan, working across the various NIH ICs that have relevant and complementary missions. NCMRR serves as the focal point for the coordination and development of policies, plans, initiatives, and objectives that further rehabilitation research, convening the NIH Medical Rehabilitation Coordination Committee (MRCC) on a monthly basis to coordinate ongoing research and training activities. In addition, MRCC works with other agencies within the Department of Health and Human Services, the Department of Veterans Affairs, the Department of Defense, and the National Science Foundation to develop collaborative projects that serve to enhance and encourage rehabilitation science. A major conference on rehabilitation research in May 2016 will bring together scientists from across the rehabilitation research spectrum, which will serve to inform and catalyze the research community through a new rehabilitation research plan, expected in early fiscal year 2017.

Training Opportunities in Endocrinology.—NICHD's intramural researchers also engage in regular collaborations with scientists from other ICs. Together with the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Dental and Craniofacial Research, NICHD collaborates on the Inter-Institute Endocrinology Training Program, an accredited program that provides a comprehensive training experience for physicians who seek a broad education in both research and clinical endocrinology. Led by world-renowned experts in the field, trainees can learn how to manage a wide variety of common and rare endocrine disorders. For example, the program provides training in specialized diabetes clinics to teach how to provide intensive insulin therapy in pediatric patients with severe diabetes.

IDeA States Pediatric Clinical Trials Network.—Following the closing of the National Children's Study in late 2014, passage of the National Pediatric Research Network Act, and after extensive input from the research and other stakeholder communities about pediatric research priorities, NIH decided to augment its pediatric research efforts through the creation of a new national pediatric network, the IDeA States Pediatric Clinical Trials Network (ISPCTN). The new ISPCTN will utilize the Institutional Development Awards (IDeA) Program, which was authorized and funded by the Congress to broaden the geographic distribution of NIH funding across the United States by enhancing the ability to compete for funding of institutions located in States in which the success rate for NIH grant applications historically has been low. The goal of ISPCTN is to develop a pediatric research infrastructure and build capacity at academic institutions in IDeA States for pediatric clinical trials; increase access to clinical trials for children (some of whom may have rare conditions) in rural and medically underserved areas who are unable to travel long distances; and allow researchers across the country who are conducting pediatric clinical trials to recruit a greater diversity of pediatric participants in a cost-effective manner. By creating teams of pediatric clinical trial specialists in IDeA States throughout the country, children who have never before had realistic access to cutting edge research will have the opportunity to participate. In addition, investigators conducting any IRB-approved, funded pediatric clinical trial (not only those in the IDeA States) may work with the Data Coordinating and Operations Center to recruit additional pediatric participants from IDeA State sites for their trials; thus, trials on rare conditions may be able to complete recruitment within a shorter period of time, even though there might be a limited number of individuals in any one geographic area. ISPCTN will be overseen by the Program Director for the new En-

vironmental influences on Child Health Outcomes (ECHO) program in the NIH Office of the Director, and managed by NICHD.

Zika Virus.—The rapid spread of the Zika virus across the Americas has emerged as a potentially critical public health issue. Although the virus was initially discovered in 1947, recent reports from Brazil suggested a possible connection with an increase in severe birth defects, including microcephaly, which sounded the alarm to the public health community. NICHD is coordinating with and contributing to the overall effort by providing expertise in developmental biology, pregnancy, and preventive measures such as contraception. Efforts include work to understand how the virus is transmitted and how best to prevent it; the effects of the virus on the body, especially during pregnancy and timing of the infection; the impact on the developing fetus; new assays to test therapeutic candidates, and improved diagnostics to rapidly identify the virus and distinguish it from related viruses. Joined by six other NIH ICs, NICHD issued a rapid funding opportunity announcement to stimulate research on Zika, particularly on the seminal issue of whether the virus causes fetal abnormalities and pregnancy complications (fetal loss, stillbirth, microcephaly, ventriculomegaly, brain anomalies, and ocular abnormalities). In addition, NICHD is coordinating with the National Institute of Allergy and Infectious Diseases and sites in several countries, including Brazil, to conduct a prospective longitudinal study on Zika-related adverse pregnancy and infant outcomes. Since evidence of a link between the Zika virus and microcephaly and other abnormalities is now sufficiently strong, NICHD will again be called upon to utilize its knowledge base on the long-term consequences of physical and intellectual disabilities to help children and families affected by the consequences of the disease.

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

Mr. Chairman and Members of the Subcommittee: I am pleased to present the President's fiscal year 2017 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 and the Intramural Research program. The OD stimulates specific areas of research to complement the ongoing efforts of NIH Institutes and Centers (ICs) through the activities of several cross-cutting program offices. The OD 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 and financial management, personnel, property, and procurement services, ethics oversight, and the administration of equal employment policies and practices. The fiscal year 2017 budget request also will 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.

The functions and initiatives of the OD's research offices, also known as Program, Projects, and Activities, are described in detail as follows:

DIVISION OF PROGRAM COORDINATION, PLANNING, AND STRATEGIC INITIATIVES

DPCPSI (Division of Program Coordination, Planning, and Strategic Initiatives) 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, research infrastructure, and science education. DPCPSI serves as a resource for 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.

OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS

ORIP (Office of Research Infrastructure Programs) 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 information, and human biospecimens. ORIP also makes grant awards to fund the purchase of expensive state-of-the-art scientific instruments and to modernize animal research facilities. ORIP supports training and career development for veterinarians engaged in biomedical research, and the diversity of the future biomedical workforce by investing in pre-kindergarten to grade 12 and museum-based science education programs.

Science Education Partnership Awards

The goal of the Science Education Partnership Awards (SEPA) program is to invest in educational activities that enhance the early training of a workforce to meet the Nation's biomedical, behavioral, and clinical research needs. The SEPA program encourages the development of innovative educational activities for pre-kindergarten to grade 12 (P-12), teachers and students from underserved communities with a focus on Courses for Skills Development, Research Experiences, Mentoring Activities, Curriculum or Methods Development or Informal Science Education (ISE) exhibits, and Outreach activities. The SEPA program will be coordinated with the Department of Education to ensure that program activities are aligned with ongoing P-12 reform efforts included in the fiscal year 2017 President's Budget request.

OFFICE OF AIDS RESEARCH

OAR (Office of Aids Research) plays a unique role at NIH by serving as a model of trans-NIH planning and management, vested with primary responsibility for overseeing all NIH AIDS-related research. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. OAR's response to the AIDS epidemic requires a unique and complex multi-institute, multi-disciplinary, global research program. This diverse research portfolio demands an unprecedented 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.

Office of Behavioral and Social Sciences Research

OBSSR (Office of Behavioral and Social Sciences Research) furthers the mission of NIH by emphasizing the critical role that behavioral and social factors play in health, healthcare, 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.

OFFICE OF RESEARCH ON WOMEN'S HEALTH

Since its creation in 1990, ORWH (Office of Research on Women's Health) has worked to ensure the inclusion of women in NIH clinical research, advance and expand women's health research, and promote advancement of women in biomedical careers. ORWH is the focal point for NIH women's health research and works in partnership with ICs to incorporate a women's health and sex differences research perspective into the NIH scientific framework. ORWH activities are guided by the 2010 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.

OFFICE OF DISEASE PREVENTION

ODP (Office of Disease Prevention) 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. Research on disease prevention is an important part of the NIH mission because the knowledge gained from this research leads to stronger clinical practice, health policy, and community health programs. In early fiscal year 2014, ODP released its first strategic plan. This plan outlines the priorities that ODP will focus on over the next 5 years and highlights

ODP's role in advancing prevention research at 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.

OFFICE OF STRATEGIC COORDINATION AND THE COMMON FUND

OSC (Office of Strategic Coordination) manages the Common Fund (CF), working with trans-NIH teams for each of the more than 30 CF programs. These teams ensure that each program meets the criteria of CF programs to synergize with IC-funded research. CF was created by the 2006 NIH Reform Act, which codified the approach of the NIH Roadmap for Medical Research to support cross-cutting, trans-NIH programs that require participation by at least two ICs or would otherwise benefit from strategic planning and coordination. CF programs tackle major challenges in biomedical research that affect many diseases or conditions or that broadly relate to human health. CF provides limited-term funding for goal-driven, coordinated research networks to generate data, solve technological problems, and/or pilot resources and tools that will stimulate the broader research community.

INTRAMURAL LOAN REPAYMENT AND SCHOLARSHIP PROGRAMS

The mission of ILRSP (Intramural Loan Repayment and Scholarship Programs) is to develop and manage programs that offer financial incentives and other benefits to attract highly-qualified physicians, nurses, and scientists into careers in biomedical, behavioral, and clinical research as employees of NIH. There are two education programs offered: the Intramural Loan Repayment Program (ILRP) and the NIH Undergraduate Scholarship Program (UGSP).

ILRP repays outstanding eligible educational debt for NIH Full-Time Equivalent employee postgraduates, and in return, participants must enter into a contractual agreement to conduct qualified research in the three statutorily governed targeted ILRPs: (1) the AIDS Research ILRP; (2) the Clinical Research ILRP for Individuals from Disadvantaged Backgrounds; and (3) the General Research ILRP.

UGSP offers competitive scholarships to exceptional undergraduate college students from financially disadvantaged backgrounds. Awardees must be committed to biomedical, social or behavioral science health-related research career paths available at NIH. Award recipients also are obligated to work as employees of the NIH Intramural Research Program in exchange for each year or partial year of scholarship funding.

PREPARED STATEMENT OF DANIEL G. WHEELAND, DIRECTOR, OFFICE OF RESEARCH FACILITIES AND DEVELOPMENT OPERATIONS, OFFICE OF THE DIRECTOR

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2017 budget request for the Buildings and Facilities (B&F) appropriation of the National Institutes of Health (NIH).

CRITICALITY OF FACILITIES TO THE RESEARCH MISSION

NIH strives to strike a balance between the infrastructure needs of tomorrow's research to address a broad spectrum of emerging health threats and the need for responsible stewardship of our real property assets supporting the research enterprise. State-of-the art facilities for scientific research and research support facilities are critical to the continuing vitality of basic, translational, and clinical research. The B&F program supports the design, construction, repair, and improvements of the NIH's portfolio of laboratory, clinical, animal, administrative, and support facilities at its six campuses in four States. These facilities house NIH researchers conducting intramural, basic, translational, and clinical research programs, science administrators who oversee NIH grant and research contract programs, the NIH leadership, and various programs that support NIH's operations. The fiscal year 2017 B&F budget request focuses on the need for responsible use and stewardship of NIH's past and recent investments in the "bricks and mortar" of the research enterprise. In addition, this budget seeks to minimize the growing backlog of maintenance and repairs required to sustain the condition of existing facilities to prevent further deterioration and, over time, further decreases to the Condition Index of our existing facilities. To stay abreast of the changing needs of the NIH programs, it is imperative that we provide reliable, safe, and secure research support facilities that are appropriately equipped, operated, and maintained.

The B&F budget request is the product of a comprehensive, corporate capital facilities planning process. It begins with extensive consultation across the research community by professional facilities staff, which results in identifying the most critical NIH facility needs. We analyze, prioritize, and submit these facility needs to the Facilities Working Group, an advisory committee to the NIH Steering Committee, and the HHS Capital Investment Review Board. Through this process, NIH prioritizes its facilities investments in order to assure safe, reliable, energy efficient and maintainable facilities to support current and emerging biomedical research.

The fiscal year 2017 B&F budget request provides funds for specific repair and improvements projects that resulted from the aforementioned NIH facilities planning process.