

**DEPARTMENTS OF LABOR, HEALTH AND
HUMAN SERVICES, AND EDUCATION, AND
RELATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2019**

THURSDAY, MAY 17, 2018

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

The subcommittee met at 10:02 a.m. in room SD-124, Dirksen Senate Office Building, Hon. Roy Blunt (chairman) presiding.

Present: Senators Blunt, Alexander, Moran, Capito, Hyde-Smith, Murray, Durbin, Reed, Shaheen, and Murphy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

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

ACCOMPANIED BY:

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

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

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

NORMAN E. SHARPLESS, M.D., DIRECTOR NATIONAL CANCER INSTITUTE

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.

We are glad to have our friends from NIH (National Institutes of Health) here today: Dr. Collins and the Institute Directors.

Recent support, I think, of medical research from our subcommittee and the full committee and the Congress is clear. During the 3 years that Senator Murray and I have worked together on this committee, we have increased funding for the National Institutes of Health by 23 percent, \$7 billion above where we were just 3 years ago. We have nearly tripled the Alzheimer's research amount, started the Precision Medicine Initiative, and targeted re-

sources to such revolutionary projects as the BRAIN Initiative, the universal flu vaccine, and efforts to combat antibiotic resistance.

A renewed investment in NIH has provided and can provide millions of Americans and their families with hope that they would not otherwise have. NIH-funded research has raised life expectancy, vastly improved the quality of life for all Americans. And in addition, I am hopeful that we can see ways to lower healthcare costs and to create economic growth by supporting the jobs, the research and the innovation that are such an important part of dealing with healthcare issues now.

Both this administration and the last one have proposed cuts in NIH funding. There is rarely a straight line in success, but so far, we have been able to maintain an upward momentum in the opportunity that I think everybody on this subcommittee certainly sees at the moment we are in.

In addition to that, things around the world like the West Africa challenge 3 years ago with the devastating outbreak of Ebola, the disease killed more than 11,000 people in Africa, became a major public health threat in the United States, and both NIH and CDC (Centers for Disease Control and Prevention) were an important part of responding to that. We see now another outbreak in the Democratic Republic of Congo. There was more news on that topic even this morning, and we need to be well prepared to continue to be able to do what we need to do to respond to those kinds of challenges.

Earlier this month, the National Institutes of Health launched enrollment in the *All of Us* study, which will collect health information from 1 million Americans, an idea that Dr. Collins mentioned, I think, 2 years ago for the first time as an NIH goal. *All of Us* has the potential to unlock precision medicine for the majority of diseases that we suffer from today. This initiative has the potential to change our health system from one-size-fits-all to really understanding more about personalized medicine.

We are also at a point where we see some drug repurposing happening. We are testing current drugs that we know are safe to see what other uses we might find in those drugs. There is a current clinical trial targeting the most common adult leukemia with a drug first approved to test arthritis more than 25 years ago. That particular work is being done at the University of Kansas. Certainly Senator Moran has been a real advocate for NIH research, and he and I hope to visit The University of Kansas Medical Center before too long and look at that project, along with others.

The National Academy of Sciences published a report in February that shows that NIH funding contributed to every one of the 210 new drugs approved by the Food and Drug Administration from 2010 till 2016. That is quite a record, and we appreciate the fact that that work continues.

We see increased grants among young researchers. Anything you have to say about that would be welcome. But this has been an effort that this committee has entered into together, and Senator Murray has been a great partner in NIH, as we hope to be appropriately involved in our oversight responsibilities as well.

[The statement follows:]

PREPARED STATEMENT OF SENATOR ROY BLUNT

Good morning. Thank you, Dr. Collins and the Institute Directors, for appearing before the Subcommittee today to discuss the National Institutes of Health's fiscal year 2019 budget request.

My support for medical research is clear. During my time as Chairman of this Subcommittee, I am proud to have increased funding for the National Institutes of Health by 23 percent, or \$7 billion, in the last 3 years. This investment nearly tripled funding for Alzheimer's research, started the Precision Medicine Initiative, and targeted resources to such revolutionary projects as the BRAIN Initiative, a universal flu vaccine, and efforts to combat antibiotic resistance.

I stand by an investment in NIH because it has provided millions of Americans and their families with hope. NIH-funded research has raised life expectancy and vastly improved the quality of life for all Americans. In addition, it has lowered healthcare costs and spurred economic growth by supporting jobs in research and generating biomedical innovations.

However, I understand that it is difficult to always quantify success in medical research. Both this Administration and the last one has proposed cuts to NIH. There is rarely a straight line to success. Not every grant funded will result in a breakthrough. However, this is not the time to abandon our commitment to medical research. The advances made in just the past 3 years is example enough to show why funding for the NIH is so important.

Three years ago, West Africa faced one of the most devastating infectious disease outbreaks of the last 50 years—Ebola. This disease killed more than 11,000 people in Africa, and became a major public health threat in the United States. Now, the Democratic Republic of Congo faces another Ebola outbreak. In response, the World Health Organization will deploy an Ebola vaccine that appears to provide protection for 2 years. This has been made possible, in part, due to the support of the National Institutes of Health.

Earlier this month, the NIH launched enrollment into the All of Us study which will collect health information from one million Americans. All of Us has the potential to unlock precision medicine for the majority of diseases we suffer from today. This initiative will change our health system from one-size-fits-all to personalized medicine.

It is also important to point out discoveries in the revolutionary work of drug repurposing—testing current drugs we know are safe for other uses. There is a current clinical trial targeting the most common of adult leukemia with a drug first approved to treat arthritis more than 25 years ago.

These are just a few examples of how investing in medical research can save lives and shows that this is not the time to back away from our support. As further evidence of the benefits of these investments, the National Academy of Sciences published a report in February that showed that NIH funding contributed to every one of the 210 new drugs approved by the Food and Drug Administration (FDA) from 2010–2016. Let me say that again. Every single drug approved by the FDA over a 6-year period had some NIH research associated with it.

The increased funding over the past 3 years, has also allowed the best researchers in the country to have their research funded to discover the next breakthrough. I am proud to say that the number of grants have increased 2,200 during this period. We finally are in a pattern of long-term investment in medical research.

I have worked closely with Senator Murray and other Members of the Subcommittee to prioritize our commitment to NIH. I know that we will continue to do so this year.

Thank you for being here today.

Senator BLUNT. But let me turn to Senator Murray for her comments.

STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Well, thank you very much, Mr. Chairman.

Dr. Collins, it is great to see you again too and all of your amazing team. Thank you all for being here today. And I just want to say it is a pleasure to see Ann Houser back there as well. She has done a lot to support our subcommittee's work for many years. She is a great credit to the agency, and I wanted to recognize her back there as well.

President Trump's budget for fiscal year 2019 once again seeks deep cuts across the spectrum of health activities, including a reduction to the National Institutes of Health that would cut its funding down to roughly \$100 million below the 2017 enacted level. That request is out of step with the sentiments of Congress and the country.

Less than 2 months ago, Congress passed and President Trump signed into law a bipartisan bill that increased funding for NIH by \$3 billion, the second largest increase in the agency's history. Those funds will be used to accelerate efforts to discover cures to Alzheimer's, cancer, and other diseases, tackle the opioid addiction crisis, and develop a universal flu vaccine, and new antibiotics and more.

President Trump's request would undermine these efforts slowing their progress.

By comparison in just the past 3 years, Congress has provided NIH an overall increase of \$7 billion boosting its budget by almost a quarter. After adjusting for inflation, the NIH budget still falls short of its peak in 2003 and grants remain highly competitive, especially for our early stage investigators, but the numbers are trending in the right direction. I am hopeful in the bill our subcommittee will shortly begin writing, we will be able to continue closing the gap. I know that Chairman Blunt feels the same way, and I want to thank him for his work on this.

These funding increases reflect a sustained commitment to invest in medical research with the goal of achieving breakthroughs that benefit all of us, including those who have been historically underrepresented in clinical research, and preserve our Nation's leadership in biomedical research. We are in a time of immense promise and challenge for the research community, the promise of unprecedented new tools, technologies, and computational power balanced by the challenge of making the most of the staggering and ever-growing amount of data that NIH produces, the BRAIN Initiative efforts to cure Alzheimer's disease, the Cancer Moonshot, and the All of Us initiative to advance precision medicine that are massive undertakings that pose extraordinary challenges, how to manage and make sense of it all, allow the research community to leverage it as much as possible, and find that proverbial needle in an immense haystack, while at the same time ensuring each patient's data remains secure.

I believe that much of NIH and its grantees are up to this task. I see the potential every time I visit the Allen Institute for Brain Science in Seattle, but few organizations have their level of sophistication.

2 years ago, the committee tasked NIH with developing a strategic plan for outlining how it would manage and make the most of the data it is producing. NIH released that plan earlier this month on schedule, but the real work lies ahead. I am concerned there still remains no senior member of the leadership responsible for that portfolio. I see that NIH recently posted an opening for a chief data strategist and understand you are actively reaching out to those in the private sector in the hope of attracting the right person to public service. It is essential we find them quickly, bring them on board, and make sure you properly support them to imple-

ment your strategic plan. I look forward to hearing more about NIH's plans in this area when we turn to the questions.

I am pleased the administration's fiscal year 2019 budget abandoned its ill-conceived proposal to drastically cut grant support funding that it proposed last year, but troubled that it now seeks to arbitrarily slash researchers' salaries by 20 percent. The budget claims this proposal would stretch grant dollars to fund more research, but like the previous proposal, it is blindly destructive and short on details, a gimmick not meant to be taken seriously.

I see the budget follows Congress' lead by preserving the increase we provided to address opioid addiction and spur the development of non-addictive pain treatments. These are critical investments of great importance to the members of this subcommittee, and I think I can speak for all of us in saying we expect NIH to make the most of those resources entrusted to address this crisis. We and those we represent are really counting on you on this one.

Finally, few agencies enjoy greater trust than the National Institutes of Health. So it was particularly troubling that questions have been raised about the impartiality of a study to assess the health benefits of moderate alcohol consumption. Dr. Collins, I know you have been focused on determining the facts with this and ensuring the integrity of NIH's research practices, and hopefully you will provide us with an update on that.

Thank you very much, Mr. Chairman.

Senator BLUNT. Thank you, Senator Murray.

I am glad again to welcome Dr. Francis Collins, the Director of the National Institutes of Health and the Institute Directors that are here with him today. I think the new Director of the National Cancer Institute, Dr. Ned Sharpless, is here for his first appearance before the committee, and we are glad you are part of this team and look forward to the chance to visit with all of you later.

But, Dr. Collins, glad to have your testimony right now.

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

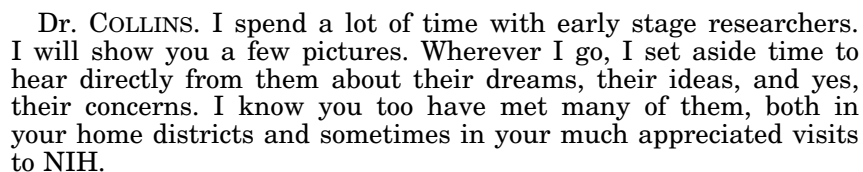
Dr. COLLINS. Well, it is an honor to be here, Mr. Chairman.

Also with me here at the table: Dr. Nora Volkow, at my left, your right, the Director of the National Institute on Drug Abuse. You mentioned Dr. Sharpless, our newbie, to my right. Walter Koroshetz, Director of the National Institute of Neurological Disorders and Stroke; next to him, Dr. Richard Hodes, Director of the National Institute on Aging; and over at the far end, somebody you know pretty well who is in his 439th hearing or something like that—

[Laughter.]

Dr. COLLINS [continuing]. Dr. Anthony Fauci, who is the Director of the National Institute of Allergy and Infectious Diseases.

I just want to say to all of you, Chairman Blunt, Ranking Member Murray, and all the friends of NIH that are here today, thank you. You have gone above and beyond in your support of NIH research and the patients for whom it brings healing and hope. In behalf of all of them, I am immensely grateful for your consistent support, and the words you have just spoken give me a great sense of confidence that we are on a very good and strong path towards the future.



[The graphics follow:]





Photo: Ted S. Warren/Associated Press



Photo: courtesy Angela Pierce

Dr. COLLINS. As we move forward with implementing the fiscal year 2018 budget and you begin considering the fiscal year 2019 request, it is a good time to think about those early stage researchers to ask what are we doing to foster this next generation of discovery and what can we do to help our Nation remain the world leader in biomedical innovation.

[The graphic follows:]

Keys to Success In Science Today

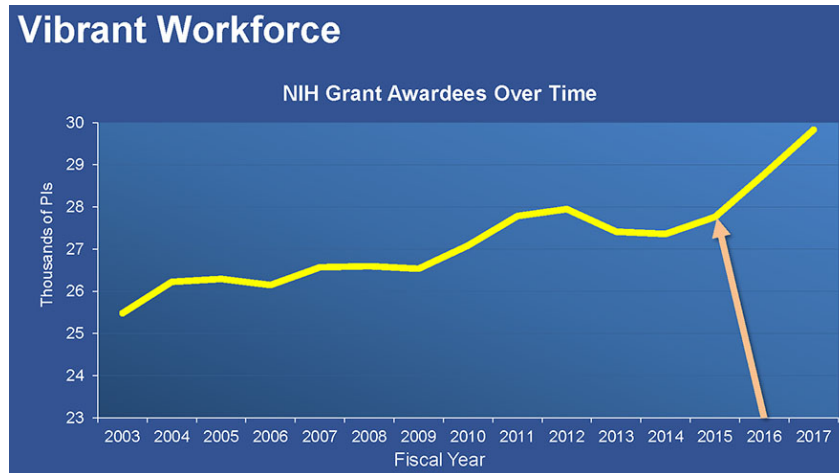
- Stable Trajectory of Support
- Vibrant Workforce
- Computational Power
- New Technologies and Facilities
- Scientific Inspiration



Dr. COLLINS. I believe the answers could be said to lie in certain key areas, and I would call them the five keys to success in science today. They are, first and foremost, a stable trajectory of support, followed by a vibrant workforce, computational power, new technologies and facilities, and perhaps most important of all, scientific inspiration.

[The graphic follows:]

Vibrant Workforce



Dr. COLLINS. The good news is that, thanks to you, early stage researchers are now beginning to see a stable trajectory of support. Your work over the last 3 years is helping us begin to reverse a distressing decade-long decline in NIH's purchasing power for research, which is carried out in every State of the Nation. Strong, stable public support lies at the heart of NIH science, and of course, that is absolutely vital to our second key to success, a vibrant workforce. Clearly success cannot lie simply in boosting the number of grants made. It must also include increasing the number of creative minds that are receiving those grants.

So I want to show you a new metric we are using to evaluate success. This shows the trend in the number of individual principal investigators supported by NIH over the past 15 years. As you can see, that number is once again growing nicely. Note especially the surge that occurs around 2016, a surge that reflects when you began to change the trajectory of NIH support, and shows how that investment in NIH science is starting to pay off.

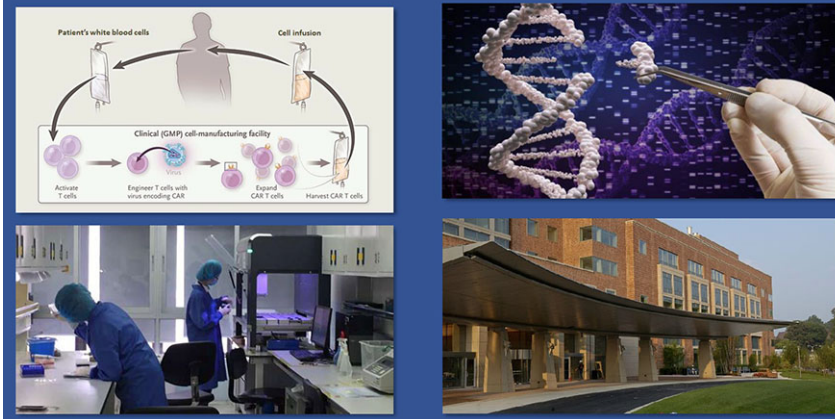
[The graphic follows:]



Dr. COLLINS. The third key to success, already mentioned by Senator Murray, is computational power. Like so much else, biomedical research has been transformed by the recent explosion in computing power and all of the big data it is generating. For example, the BRAIN Initiative, which you have supported for the past 5 years, has created new imaging tools that are churning out troves of amazing data, and there is also data generated by structural biology and microbiome research and the All of Us research program supported by your precision medicine appropriation. Just 10 days ago in a major national launch event, all of us began the full scale of enrolling 1 million Americans, building on their pilot phase that already enrolled over 25,000, aiming to determine how individual differences and lifestyle, environment, and biological makeup can influence health and at an unprecedented scale.

[The graphic follows:]

New Technologies and Facilities



Dr. COLLINS. To realize the full potential of these and other resources, we also must develop new technologies and facilities. Quite often it is the technology itself driving the need for equally innovative facilities. Take the case of the new cell-based treatments, immunotherapy and gene therapy. Many involve removing cells from the patient's body using technology to re-engineer those cells and returning them to the patient. The challenge is that many of our labs are not set up to handle these highly individualized processes, so it is crucial that we make upgrades to keep pace. The President's fiscal year 2019 proposal includes a much needed increase in buildings and facilities to assist with that.

[The graphic follows:]

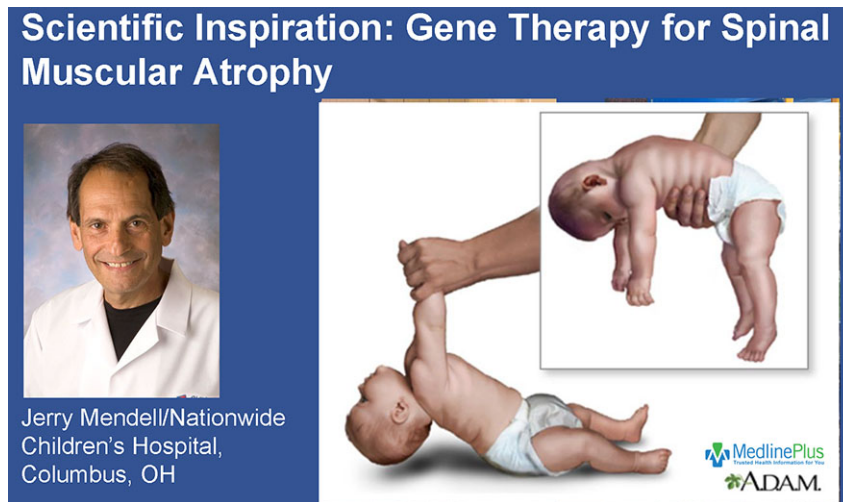
Scientific Inspiration



Dr. COLLINS. But now on to my favorite of these topics, scientific inspiration. I can assure you that NIH-funded researchers come to work every day full of innovative ideas and the wherewithal to see

those ideas through. I could talk about this all day, but mindful of the clock, let me just share one example.

[The graphic follows:]



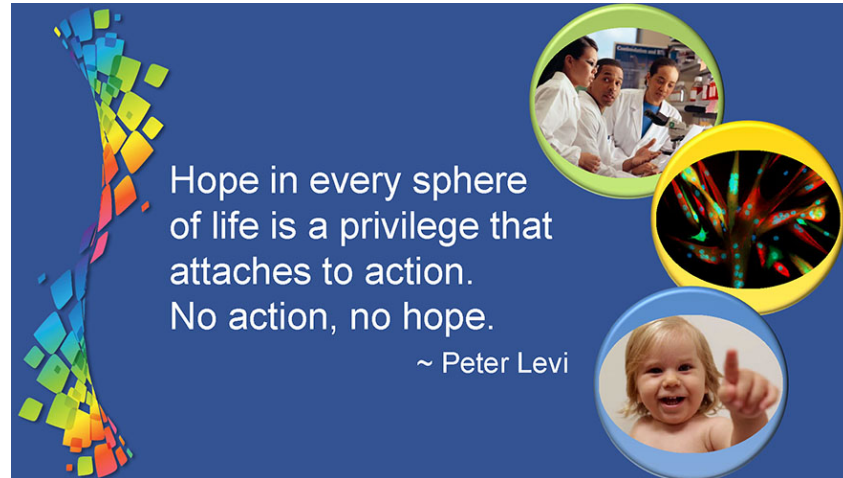
Dr. COLLINS. More than a decade ago, NIH launched a special project on spinal muscular atrophy, or SMA. This is a uniformly fatal inherited disease. As you see here, in its severe form, it leaves babies floppy, unable to hold their heads up, feed well, and eventually even to breathe. Death by 15 months is the tragic and almost universal result.

10 years ago there was no treatment for SMA, but researchers had just discovered the DNA (deoxyribonucleic acid) mutations that cause it. So NIH supported more research, working closely with patient advocates and industry to move promising leads into therapeutic development. One of the most exciting comes from Jerry Mendell's team at Nationwide Children's Hospital in Columbus, Ohio, which recently tested gene therapy in 15 infants with severe SMA. They infused the viral vector designed to deliver the normal gene to the spinal cord and held their breath.

And over the next few months, something truly dramatic, almost miraculous, happened. Like little Mateo Almeda, whom you see in this video, 100 percent of the infants who got the highest dose of the gene therapy were alive at 20 months and nearly all could talk and eat on their own, and some like Mateo, shown here at age 2 standing up on his tiptoes, were able to walk—and this is truly astounding—even play on the monkey bars with his dad. As a direct result of an NIH-inspired effort, we are seeing the emergence of lifesaving gene therapy for SMA.

So in closing, I am proud to lead NIH at this time of unprecedented scientific opportunity and with such strong congressional support. The resources you have entrusted to us will be used to bring hope to untold numbers of patients and their families.

[The graphic follows:]



Dr. COLLINS. In that spirit, I would like to finish with a favorite quote from the poet Peter Levi. “Hope,” he wrote, “in every sphere of life is a privilege that attaches to action. No action, no hope.” At NIH our idea of action is to support the best investigators to apply the best science to find answers for those millions waiting for their hopes to be realized.

Thank you, and I look forward to 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. I am Francis S. Collins, M.D., Ph.D., and I have served as the Director of the National Institutes of Health (NIH) since 2009. It is an honor to appear before you today.

Before I discuss NIH’s diverse investments in biomedical research and some of the exciting scientific opportunities on the horizon, I want to thank this Subcommittee for your sustained commitment to NIH to ensure that our Nation remains the global leader in biomedical research and advances in human health.

I want to personally express gratitude to this Subcommittee and its leadership for its support in crafting and passing the fiscal year 2018 Consolidated Appropriations Bill. The fiscal year 2018 Omnibus provides an incredible increase of \$3 billion for NIH, including funding for opioid- and pain-related research, Alzheimer’s disease, antimicrobial resistance, and development of a universal influenza vaccine. NIH has immediately set to work to invest those additional resources into groundbreaking research.

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. As some of you have witnessed first-hand on your visits to NIH, our leadership and employees carry out our mission with passion and commitment. This extends equally to the hundreds of thousands of individuals whose research and training we support, located in every State of this great country, and where 81 percent of our budget is distributed.

The fiscal year 2019 Budget provides \$34.8 billion for NIH to fund the highest priority scientific discoveries while also maintaining fiscal stewardship of Federal resources. This Budget will consolidate research functions across the Department, optimize available grant dollars to fund research, invest in NIH’s buildings and facilities, and support NIH priority areas including combatting the opioid epidemic, advancing Precision Medicine, and investing in translational research.

The fiscal year 2019 Budget consolidates HHS research programs into three new institutes within the NIH. The Budget provides \$380 million for the activities of the

Agency for Healthcare Research and Quality (AHRQ), consolidated into the National Institute for Research on Safety and Quality. The National Institute for Occupational Safety and Health (NIOSH), including the Energy Employees Occupational Illness Program (EEOCIPA), currently administered by the Centers for Disease Control and Prevention, and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR), currently administered by the Administration for Community Living, are also proposed for consolidation into the NIH.

America's continuing leadership in conducting biomedical research requires infrastructure and facilities that are safe, compliant with all laws and regulations, and conducive to cutting edge research and research support. NIH owns 281 facilities, including a research hospital, laboratories, and offices. NIH's Backlog of Maintenance and Repair exceeds \$1.8 billion. NIH is currently working with the National Academies of Sciences, Engineering and Medicine to identify NIH facilities and infrastructure most in need of repair. We look forward to providing that report to the Committee as soon as it is final.

The fiscal year 2019 Budget makes much needed investments in NIH's facilities. The Budget proposes \$200 million to support multiple biomedical research infrastructure priorities. The fiscal year 2019 Budget will allow NIH to continue to repair and upgrade deteriorated infrastructure. In a recent analysis requested by this Committee, the condition of NIH laboratories ranks near the lowest in the Federal Government due to the high likelihood of floods, power outages, and mechanical failures. Items on the backlog list include: install steam and chilled water distribution systems; conduct structural repairs to older buildings; upgrade plumbing systems; repair elevators; upgrade heating, ventilating, and air conditioning systems; replace deteriorated electrical systems, and more. In addition, due to the age and use of NIH facilities, NIH must invest funds in removing contaminants and hazardous waste before construction or capital repairs can begin in most of its buildings. The Budget will allow NIH to track what contaminants are being cleared from each of our buildings, which will ultimately help NIH do a better job of anticipating the cost and time required to begin new projects in existing buildings.

Truly exciting, world class science is taking place. I would like to provide just a few examples of the depth and breadth of the amazing research the fiscal year 2019 Budget supports across the Institutes and Centers of NIH.

Over the past 15 years, communities across our Nation have been devastated by increasing prescription and illicit opioid misuse, addiction, and overdose. This Committee made a historic investment of \$500 million in our work in fiscal year 2018, and the fiscal year 2019 Budget builds on that with an investment of \$850 million to support a range of activities to advance research on pain and addiction. NIH has and will continue to support cutting-edge research on pain, opioid misuse, addiction, and overdose. Drug addiction is a complex neurological condition, driven by many biological, environmental, social, and developmental factors. Continued research will be key to understanding the crisis and informing future efforts. Pain is an equally complex condition affecting millions of Americans. NIH will: explore new formulations for overdose reversal medications capable of combatting powerful synthetic opioids; search for new options for treating addiction and maintaining sobriety; continue to research how best to treat babies born in withdrawal through our ACT NOW trial; develop biomarkers to objectively measure pain; build a clinical trial network for pain research; and attempt to find non-addictive and non-pharmacological approaches to chronic pain. Thanks to your support, all hands are on deck at NIH for this public health crisis.

Another exciting area of continued investment in fiscal year 2019, building on this Committee's long-standing support, is Precision Medicine. On May 6th, NIH officially launched the national roll-out of the All of Us Research Program. This program will partner with one million or more people across the United States to provide the most diverse biomedical data resource of its kind and gain unprecedented insights into the biological, environmental and behavioral influences of disease. The fiscal year 2019 Budget, including resources from the 21st Century Cures Act, supports the ramp up of the program. After pilot testing system and forming partnerships with community organizations across the country, national enrollment is about to begin. All of Us will not focus on only one specific disease. Rather, it will be a national data resource to inform many research studies on a wide variety of health conditions. The data provided by one million participants will provide opportunities for researchers—including academics and citizen scientists—who want to understand how and why different people experience certain diseases and conditions while others do not, and why many people respond differently to treatments and prevention methods that will help accelerate medical breakthroughs.

NIH is the largest funder of basic biomedical research in the United States, providing a critical research foundation for both the public and private sector. Building

on that solid foundation of basic research, NIH also supports translational research that turns observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public, whether those interventions be diagnostics, therapeutics, medical procedures, or behavioral changes. For example, Congress created the Cures Acceleration Network (CAN) at the National Center for Advancing Translational Sciences (NCATS) to advance the development of high-need cures and to reduce significant barriers between research discovery and clinical trials. For example, CAN currently supports NCATS' Tissue Chip for Drug Screening program, which was designed to revolutionize the process for predicting drug safety. Researchers developing miniaturized platforms that could support miniature models of living organs—such as the lung, liver, and heart—that could be integrated into connected organ systems. New Tissue Chip initiatives were funded in fiscal year 2017 and this support will continue into fiscal year 2019.

CAN uses flexible research awards using the special authorization called other transaction authority to attract non-traditional government partners, and to expand, modify, and, if needed, discontinue activities to meet program needs. The fiscal year 2019 Budget will allow NCATS, through CAN, to continue to invest in high-risk, high reward initiatives designed to address significant scientific and technical challenges that hinder translational research.

One of my personal priorities is developing the next generation of talented biomedical researchers. Last year, I shared with the Committee NIH's plans to build on our support for early-stage investigators through a new initiative known as the Next Generation Researchers Initiative. The fiscal year 2019 Budget includes a dedicated fund of \$100 million in the Office of the Director to incentivize additional Institute and Center support for these researchers. NIH remains committed to the development, support, and retention of our next generation of investigators.

We have never witnessed a time of greater promise for advances in medicine than right now. Your support has been critical, and will continue to be. Thank you again for inviting NIH to testify today. We look forward to answering your questions.

Senator BLUNT. Well, thank you, Dr. Collins.

We will have 5-minute rounds of questions. There will be time for a second round if we are still in the hearing when we have the vote at 11:15. I think it is one vote. And so we will try to work around that and continue the hearing.

PUBLIC/PRIVATE PARTNERSHIPS

One of the things that we put in the appropriations bill this year was an effort that, frankly, we were asked to put in where there would be some partnership money from pharmaceutical companies into opioid research, the idea being that like other partnerships, for example, the AMP partnerships between NIH and other biopharmaceutical companies, that we could deal with that quicker. You have decided and frankly, without consultation with the committee, not to do that. It might very well relate to the alcohol study that Senator Murray brought up. I would like you to respond to both of those topics, starting with why you decided not to do what you had asked us to put in the budget to allow you to do.

Dr. COLLINS. Senator, I will be glad to explain that, and I know this is a topic that many people have been interested in and have been wrestling with a bit, as we have.

We have been in deep conversations with industry partners for a year about ways in which we might develop a partnership to come up with better ways to treat addiction, to treat overdose, and to come up with non-addictive treatments for chronic pain, which are desperately needed. Working with 33 such companies over the course of many months, we have identified a number of areas of opportunity which we could do effectively in a public-private partnership with them in ways that neither sector could do alone. And that includes such things as sharing data, sharing assets,

repurposing compounds that might have been tried for something else or have been abandoned and could turn out to be valuable for pain, and running clinical trials together in that space.

The good news is that partnership is very much alive and will, in fact, be going forward. I think we are pretty close to having the full plan laid out, and I would expect in the next few weeks to be able to say much more about exactly how we are going to conduct this.

The controversy, Senator, was whether in fact, given the circumstances around the opioid crisis and the fact that there are lawsuits now filed against no less than five of these companies claiming that they may have played some role in the opioid crisis in the first place by marketing such drugs as OxyContin, whether it is in fact a good idea or potentially carries a reputational risk for NIH to receive funds from the company.

And ultimately I convened an expert group of advisors from outside who had lots of experience in both sectors and who were very finely tuned to the questions of reputational risk and ethics. And to my surprise, they made a strong recommendation that we go forward with the partnership but not have actual cash contributions from the companies involved. Their concern was that that would create at least the impression, if not the reality that the project going forward would be in some way a conflict of interest, would be driven by something other than the best needs of the public.

I had to accept that strong recommendation coming from those groups. The Foundation for NIH, by the way, which is our partner in all of these partnerships, also convened their board and came up with the same recommendation.

And so with apologies for not having consulted, as I should have, with you and other members of this subcommittee, we felt we had to make the decision that we did.

Again, the good news is the partnership will go forward very much as planned, but we are not asking the companies to contribute money, but we are asking them to contribute expertise and resources and data and assets and help with our clinical trials network.

Yes, the alcohol issue was also in this particular discussion because we are in the midst of another place that I wish we were not where there is deep concerns about whether a study, which has really just gotten launched in the last 2 or 3 months, which aims to look at whether there might be medical benefit of modest doses of alcohol in humans. And this particular study was set up in such a way that the funding is largely coming from the beverage industry, and there is evidence that NIH employees assisted in recruiting those funds for this study in a way that would violate our usual policies.

We are in the midst of investigating that through the Office Management Assessment and through a working group that I have convened. There are sufficient concerns about that study that I would like to tell you that 1 week ago, we decided to suspend enrollment in that study of the moderate effects of alcohol on cardiovascular health while we continue the investigation and make a decision about whether the study is in fact still worth pursuing.

So all of those are complicated issues and believe me, have caused considerable pain and stress upon the people involved. But again, for NIH, our reputation is so critical, and if we are putting ourselves in a circumstance where that could be called into question, I felt we had to look at that very seriously and come up with another strategy.

Senator BLUNT. Thank you.

I could probably ask another question quickly and get way beyond my 5 minutes but I am not going to do that, and I hope nobody else will either. If you want to stay for a second round of questions, we are going to do that.

Senator Murray.

BIG DATA

Senator MURRAY. Thank you very much.

And I wanted to go back to the big data because one of the greatest challenges facing science today is how to manage and effectively use this massive amount of data that researchers are now producing, and without the tools to efficiently manage and manipulate data, the value of it is significantly reduced. Likewise, we do not want scientists spending time recreating data that already exists from other research projects. And as you know, the committee directed NIH in the 2017 omnibus to develop a strategic plan to address these issues, which you released last week.

Now that you have the plan, can you tell us what the timeline for implementation is?

Dr. COLLINS. The plan is very ambitious, Senator. And I am glad you had a chance to look at it. It is the product of many deliberations with experts both within NIH and outside and also responding to a request for comments from more than 800 individuals and organizations who put forward a plan.

Basically it does lay out what we need to be doing in the area of infrastructure, in the area of the data ecosystem, in the area of software and tools, particularly in the area of the workforce. We realize our bench is not as deep as it should be for expertise in this space, and also just sustainability, how do we put together something that is not here today and then in trouble tomorrow. All of those are laid out in the strategic plan in a broad and bold way.

The way in which we are going to implement this certainly includes a number of things that are already underway because we have really been working on this issue since 2012 when a working group of my advisory committee made the first set of recommendations. We are, for instance, moving some of our largest datasets into the cloud in a fashion that protects the security and privacy of the participants but makes that data accessible to researchers from all over the place. And that is a big step forward, and most of our big datasets will need to be handled in that way going forward.

And as you mentioned in your opening comments, we are actively recruiting for a chief data strategist, someone who we would ideally hope to recruit from industry and maybe from Silicon Valley with deep experience in how to handle big datasets and machine learning and artificial intelligence.

BARRIERS IN DATA SHARING

Senator MURRAY. Are there barriers that are worrying you like cases where researchers face challenges sharing their data or delay releasing the data until they have published their findings, things like that?

Dr. COLLINS. We are certainly attuned to the risks there of people hoarding data. I am happy to say the 21st Century CURES bill gave me as the NIH Director some authorities about requiring data access and data release from our grantees, which I used to have to do some cajoling, but now I have the opportunity to have more clout and that has helped us in that regard.

I think the general ethic of the scientific community has shifted, though, much more in the direction of it is your responsibility to make your data available as soon as someone else might be able to use it. We have encouraged that a lot.

Senator MURRAY. Okay, good.

DATA SHARING IN ALZHEIMER'S DISEASE

And Dr. Hodes, I wanted to ask you. Given the scale of investments that we are making in Alzheimer's disease, the data we are generating may be used to accelerate some major scientific breakthroughs. Has NIA (National Institute on Aging) looked at its existing data sharing policies to determine how they are working? Do we know what percentage of grant recipients are fulfilling their data sharing obligations on this project?

Dr. HODES. Thank you very much for the question.

I would echo very much what Dr. Collins has just said about NIH's role in general.

I think we have had a history in the Alzheimer's research community of a strong willingness to share, and I think that has increased over past years. I think we are at a stage when we are dealing in part with technical feasibilities of making data cross-interpretable, shareable, and compatible and are working very hard in collaborations across Federal agencies and with outside groups to make that sharing more effective. But I think we have the culture, as well as the armamentarium to enforce sharing, and I think we are on an excellent trajectory in that regard.

Senator MURRAY. Thank you.

MODERATE DRINKING STUDY

Dr. Collins, just one more question on the moderate drinking study. NIH is a huge enterprise, and if this was happening in one institute, it could be happening in others. Are you doing anything to make sure this has not compromised studies elsewhere in NIH?

Dr. COLLINS. I am very concerned that this might be the tip of a larger iceberg, and that is part of the reason that I pulled together this very distinguished group of experts to look at it. We will look closely to see if there are other examples of this sort because that would be very much against the principles that we stand for, which is separation of funding sources from outside with decisions about science, and also of course, our peer review process ought to be absolutely above any reproach as far as conflicts.

I would be glad to report back to you after we have done a bit more digging into this. But I think this is one of my roles as the NIH Director. When we find something that has gone awry, we do not just assume that it is a little thing that you could put a band aid on. We make sure that it is not reflective of some larger issues, and then we aim to fix those too.

Senator MURRAY. Thank you very much.

And thank you, Mr. Chairman.

Senator BLUNT. Senator Alexander.

Senator ALEXANDER. Thank you, Mr. Chairman.

First, let me say to Chairman Blunt and to Senator Murray, Senator Durbin, all the members of the committee, how much I appreciate their leadership and the increase in funding for the National Institutes of Health. And I pledge my support to do that for the future.

Second, it is good to see a piece of legislation that had such broad bipartisan support. Senator McConnell said it was the most important law of 2016. Actually it would be so useful in its implementation. A part of that is because of the talent of the team we see before us and others like Dr. Gottlieb who know what they are doing and are leaning forward and taking advantage of the new authority.

Third, we have developed quite a consensus on science and research. As Senator Blunt said, a 23 percent increase in biomedical innovation. I would add to that that in the Energy and Water Appropriations Subcommittee, which Senator Feinstein and I chair, we increase funding for the Office of Science this year 16 percent. That was the third straight year of record funding for the Office of Science that supports the national laboratories. So when you get 3 straight years for the National Institutes of Health, 3 straight years of record funding for the Office of Science, and you add to that in the Obama administration and in the first 2 years of this administration we have funded supercomputing at impressive levels to keep us first in the world in that, I think the only people not on board with the President's America First comments are the Office of Management and Budget.

So I am going to try to talk to the President and others at the White House and say why do you not include this in your America First agenda. I mean, why not buy medical innovation, why not national laboratories, why not supercomputing? We need to lead the world in that. Congress wants to do it, both Republicans and Democrats. We need to get the OMB (Office of Management and Budget) on board.

NON-ADDICTIVE PAIN STRATEGIES

Now, let me use the rest of my time to ask you about one area, non-addictive pain strategies. We have 25 million Americans who hurt badly, chronic pain, 100 million who hurt some, and then non-addictive treatment for opioid abuse. 95 percent of the treatment for opioids is more opioids. It is medicated assisted abuse. And sometimes they say you do not ever get off opioids.

So my question is in 2 minutes and a half, what progress are you making? Senator Murray and I have included in the opioids bill the transactional authority that you asked for to give you even more

flexibility in funding. What progress are you making on pain, new pain strategies, and why are 95 percent of the treatments for opioids more opioids? Why do we not have more treatments like Vivitrol or some other treatment that helps people get away from opioids?

Dr. COLLINS. So I am fortunate to have at the table two experts who can handle both parts of that question. Maybe we will go first to Dr. Volkow to talk about the treatments for addiction and what we might be working on in that space. And then I will ask Dr. Koroshetz to respond about non-addictive treatments for pain. We are deep into that as well.

Dr. VOLKOW. Thanks, Francis.

This is one of our priorities, how do we develop alternative medications for the management of opioid addiction. We currently only have three of them, and two of them are what we call agonists, opioid agonists. And Vivitrol is an antagonist.

Senator ALEXANDER. And I am right that two are about 95 percent of the treatment. Right?

Dr. VOLKOW. Correct. That is correct. Those are the numbers.

And part of the problem is not all of the patients respond to the Vivitrol intervention, and part of the problem is it is very difficult to induct someone that is addicted right away into Vivitrol. And that is when we lose the patients. So we are trying to expand the alternative medications that we can give to patients and focusing also on strategies that are not involved in the opioid system so that we can help those individuals be able to recover and be at one point able to stay without opioid medications.

Dr. KOROSHETZ. So I think that you are absolutely right that one thing that could really help in the long term stemming the opioid problem is developing non-addictive pain medicines to replace opioids in the prescription box for patients.

Senator ALEXANDER. And we funded \$500 million in research this past year—Senator Blunt and Murray did—and \$500 million more proposed by the budget for this coming year.

Dr. KOROSHETZ. That is right. And so we, working with our industry partners, as Francis mentioned, have a plan to really accelerate the development of new medications. From the basic science point of view, we have a number of different targets that look very promising to develop medicines that are not interacting with the opioid pathway.

One that is in current testing now is what is called anti-nerve growth factor therapy, which came from really very important basic science years ago on the intersection of that growth factor and the pain system. And companies are now developing antagonists to nerve growth factor which look promising in early results. So just one example, but we think there are many more.

Senator ALEXANDER. Thank you, Mr. Chairman.

Senator BLUNT. Senator Reed.

Senator REED. Thank you very much, Mr. Chairman.

Thank you all. I particularly want to thank Dr. Sharpless for giving me an opportunity to look at the pediatric oncology program and meeting all the tremendous women doctors and Ph.D.s who lead that effort. So thank you.

STAR ACT

With the support of another tremendous woman, Senator Capito, we were able to pass the STAR Act. And can you give us an idea of how you will use this? It will pass, we hope, the House very soon and become law.

Dr. SHARPLESS. Sure. I should not directly comment on pending legislation, but—and first off, thank you for the visit. I think it really means a lot to the pediatric oncologists to have the Senate come up and express an interest in work that they are doing and I think is really, really wonderful. And thank you for your support and Senator Capito's support of pediatric cancer research.

The STAR Act—the intent of it is very laudable to address issues, some issues in pediatric oncology and childhood cancer that are important. So one is the issue of survivorship. The good news about pediatric cancer is we are curing more and more kids, but the problem is—well, the two problems are we are not curing everyone. We still have kids die of cancer. And then a lot of the kids we cure are left with lifelong toxicity. So the results from therapy can be quite debilitating, infertility, disfiguring surgery, and cognitive dysfunction that last for decades.

So survivorship has become a major issue. There are probably half a million pediatric cancer survivors now in the United States. And trying further research to understand the basic science of survivorship and why these toxicities occur and what we can do is a really important area of pediatric oncology research.

Similarly, I think we had this issue of aggregated data in pediatric cancer. One of the shortages of that are samples, biospecimens that can be sequenced and analyzed and catalogued, and then presented to the research community in an aggregated format that is de-identified and secure but usable for research.

And so I think those two addressing survivorship and biospecimens are really important and something NCI (National Cancer Institute) is behind.

TRANS-NIH PEDIATRIC RESEARCH CONSORTIUM

Senator REED. Thank you very much.

And Dr. Collins, thank you again for your hospitality on my visit.

You have recently announced the creation of a trans-NIH pediatric research consortium. Can you give us an idea of what you want to accomplish with that, Doctor?

Dr. COLLINS. I would be very happy to.

We have the National Institute of Child Health and Human Development, which sounds like it is the place where pediatric research gets done and a lot does get there. But it is actually only about 18 percent of pediatric research across all of NIH. Most of the institutes—you have just heard a great example from the Cancer Institute—are also heavily invested in pediatric research.

I have asked Diana Bianchi who is the new Director of the Child Health Institute to convene a trans-NIH group at a high level from all of the institutes that are players, which is essentially all of them, to see whether we could come up with a more coordinated strategic plan for defining where are the greatest priorities in pediatric research and how can we work together, whether it is cancer

or whether it is autism, whether it is birth defects, whether it is development, whether it is behavioral issues. I believe with her leadership—and she is a very strong leader, indeed—that we have the chance to put forward a plan for pediatric research that will be quite exciting. That has just gotten going, and I would be glad to report back to you in the coming months about how this is leading us in new directions.

FOGARTY INTERNATIONAL CENTER

Senator REED. I would be remiss if I did not applaud the Fogarty Center, named after my beloved predecessor in the United States Congress, John Fogarty. But this is the international arm, if you will, of NIH, and we celebrated the 50th anniversary. And it seems particularly important today, as we talk about Ebola emerging in countries like this, that we have this agency in very close rapport with CDC.

Can you just comment upon the next wonderful 50 years of the Fogarty Center? And tell Peter Kilmarx I said hello.

Dr. COLLINS. Senator, I appreciated very much your being there at that 50th anniversary celebration and speaking to the group.

One of the things Fogarty has done that has been most powerful, even though it is the smallest of all of our institutes, is their training program for fellows.

I am just going to quickly ask Tony Fauci to tell you a story or two about how those Fogarty fellows have played a significant role in global health challenges like Ebola and Zika.

Dr. FAUCI. Thank you, Dr. Collins.

Yes, the Fogarty International Center really has been very important and very much interdigitated with what we do as the National Institute of Allergy and Infectious Diseases (NIAID) in the area of infectious diseases. You may recall that when we had the Ebola outbreak in West Africa in 2014, 2015, and early 2016, there were cases that, as you might expect, traveled not knowing they were infected with Ebola to other places such as Mali and Nigeria. And those cases did not result in outbreaks in those countries. Almost all the people taking care of those individuals infected with Ebola virus who traveled to Mali and Nigeria were trained as Fogarty fellows. So we had a pre-existing network of people there who had been trained in science and public health with support from the NIH. That was a dramatic public health example of how the Fogarty Center was a true partner, not only with regard to Fogarty activities on our NIH campus in Bethesda, MD but also to Fogarty activities in Bamako, Mali and Lagos, Nigeria. It was really quite striking.

Senator REED. With a speech like that, you could be elected to Congress from the 2nd district. Thank you.

[Laughter.]

Senator BLUNT. Senator Capito.

OPIOIDS PARTNERSHIP

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

And Dr. Collins, it is great to see you again.

My first question is on opioids and what you are doing. And we have talked numerous times about this. Obviously, I live in an area that is highly affected here.

Two questions. You mentioned and you said that we had put a \$500 million historic investment into this. But you have mentioned in your response to questions that you have private partners. Could you elaborate on how the private partnership works, and what kind of commitment dollar-wise that private partnership is committing to add to the \$500 million that we are doing in the research?

Dr. COLLINS. Happy to.

We have worked intensively since your wonderful decision to make \$500 million available in fiscal year 2018 and to have that in the base so that it will be there in 2019 and beyond. Working with all of the institutes across NIH, we have put forward an opportunity for new and bold ideas to come forward, and we are in a place now, I think, of having a remarkable portfolio that we are ready to launch.

You also graciously gave us that first year of support as 2-year money so that we could, in fact, carry over some of the fiscal year 2018 funds into 2019 since it is late enough in the year that starting brand new things is a little challenging. But we have figured out how we are going to spend a significant fraction of that \$500 million right away.

It does include a wide variety of applications, including some of the things that have already been discussed by Dr. Volkow and Dr. Koroshetz, but also such things as what to do about the neonatal abstinence syndrome, which is of such deep concern to all of us in terms of how best to manage, what happens to those babies, and what is their long-term future.

The public-private partnership, which you mentioned, is actually a modest part of this broad portfolio but an important one. Again, as we talked about earlier, the decision was made by me based on strong recommendations that that partnership should involve assets that are contributed by industry that have value, data, compounds, scientific expertise, but not a cash contribution. It is a little challenging right now to attach a dollar value to what their in-kind contributions are going to add up to, but it will be substantial.

Senator CAPITO. Good.

Dr. COLLINS. So putting that all together, we think we are in a good place to move both the public-private partnership and the rest of this broad portfolio together quite rapidly.

NEONATAL ABSTINENCE SYNDROME

Senator CAPITO. Good. Thank you.

Dr. Volkow, on the neonatal abstinence syndrome, obviously we are the State most highly affected by that as well. And this is an area of deep concern to everybody. We have got 1,000 more kids in foster care. A lot of these babies probably will be the repeat mothers. They have repeat exposure. I mean, they have numerous exposures to numerous drugs not just particularly one. And I believe you visited our Lily's Place down in Huntington to see what kind of care they are getting there.

The research that you are doing and the ACT NOW trials— are those being conducted across the Nation, or how do you find the

right place to conduct those kinds of—and where are you doing that?

Dr. VOLKOW. Well, the ACT NOW is one of the programs that will be funded through the new money that has come for the opioid crisis and will allow us to actually maximize protocols that will enable us, for example, to determine what are the optimal interventions for the best outcomes on neonates. And that includes protocols that may not require the administration of medications to those neonates with abstinence.

We have other research studies also ongoing. And I was at West Virginia last week and I was in Huntington. And I was horrified to hear that one out of five newborns had opioids on them. And one of the points that is highlighted is that we need to address the needs of the neonate, but we need to address the needs of the mother once the baby is born. So the outcome from that infant and child is not addressed. So we are working with research of new medications and new non-medication interventions to improve the outcomes of those neonates.

And the other aspect that Francis mentioned is we are very interested in understanding how the brain of these newborns is going to have been influenced by getting exposed to opioids, as well as other drugs, during fetal development when the brain is very, very vulnerable.

Senator CAPITO. Right. I am anxious to hear how we progress with that.

I guess one of the points of asking my question is there a wealth of data all around the country with people who are hands on in these scenarios dealing with this right now that I think can feed not only good information but can help you conduct trials on a local level. It sounds like that is what you are already moving forward on.

Dr. VOLKOW. Correct.

CLINICAL TRIALS—ALZHEIMER'S

Senator CAPITO. I am really pleased to be on the STAR Act, the childhood cancer act. I am glad to hear about the survivorship. That is something of great importance to me. A lot of this I am very interested in, as Dr. Collins knows, but I do want to go over to Dr. Hodes because Alzheimer's on the other end of the spectrum is something that I have personally been touched with.

And I would like to know, Doctor, one of the things I have heard is that it is hard to recruit patients for clinical trials for Alzheimer's. Is that the case? What are you finding there? I mean, I know it is hard by the time you start exhibiting the symptoms, you are already in it. How are you developing all those trials with different—

Dr. HODES. Senator, it is an excellent question. And it is a challenge to us for multiple reasons.

As you have commented upon, for individuals who are already affected with symptoms, we carry out studies that are extremely important. But there is also a sense that in order to be most effective in preventing the appearance of symptoms that we need to intervene earlier before irreparable damage is done.

This means that we need to recruit people who are not coming through a normal process where they see a clinician who suggests they participate in a clinical trial. These are people who are at high risk but show no symptoms. So we need to develop and are developing strategies for screening those at high risk and then the charge of finding people who are committed, dedicated to participate in studies to see if we can make a difference through early intervention.

Studies such as All of Us present a unique opportunity for this with a million people, for example, who have signed on for their interest in participating in research. We can screen those who, by a variety of metrics, may be at high risk for developing symptoms years or decades later and take an opportunity to intervene with those now. So we are in the midst of a nationwide program which will be announced this summer to look at multiple modalities for recruiting patients into studies.

Senator CAPITO. Good. Thank you. We want to support that. Thank you.

Senator BLUNT. Senator Shaheen.

FENTANYL

Senator SHAHEEN. Thank you, Mr. Chairman.

And thank you to you and Senator Murray and Senator Alexander for your commitment to research and funding for NIH.

And to you, Dr. Collins, and everyone there, thank you so much for the work that you are doing. You give hope to so many people across this country.

Dr. Volkow, thank you for coming to New Hampshire. I especially appreciate the work that is being done to address the opioid epidemic. Like my colleagues on this committee, we have been very hard hit in New Hampshire, as you know, from your visit to Catholic Medical Center and other places in the State.

I was interested in your discussion about new drugs that are in development. As you are looking at what the potential is, are you separating out fentanyl as a particular opioid that has very deadly properties and therefore requires a different kind of response, or are you lumping that in with everything else?

Dr. VOLKOW. We cannot lump it with everything else because what we are hearing from the field and being reported in the literature is that when people overdose with fentanyl, the doses that were used of Narcan are not sufficient actually to reverse the overdoses. The other concern is if you get exposed to fentanyl, because of its potency, your risk of addiction is much higher.

So as of now, we, for example, have not ever done a trial of how do you treat someone that is addicted to fentanyl, and that is one of the projects that we would like to implement as soon as we get the approvals.

But also with respect to the medications, we are actually funding researchers who are partnering with pharmaceuticals to develop a stronger antagonist. So this is the nasal Narcan, which we actually developed, but it is not sufficient for fentanyl. So we are developing with companies longer lasting, more potent or alternative medications that may not be based on the same mechanism as naloxone. Because the other challenge is not just fentanyl, but what we are

observing is people are overdosing with multiple medications, alcohol, benzodiazepines, and fentanyl. So this is not sufficient.

CO-OCCURRING MENTAL HEALTH ISSUES AND SUBSTANCE ABUSE

Senator SHAHEEN. And we see so many people who have co-occurring mental health issues along with their substance use disorder. So often they are using substances to address their mental health issues.

So are you doing any research that looks at the two problems together that may give promise as we think about what the future holds?

Dr. VOLKOW. We cannot do that because the comorbidity is many times much more frequent, the isolation. And if you address, for example, the depression of someone that is addicted to opioids, you are not going to succeed.

Also a very important component followed by the overdose is we really do not know which ones are intentional, therefore suicide. So if you are reverting someone on an overdose that has suicidal behavior and you do not intervene, you are not going to succeed.

So we are prioritizing. We are recognizing that the reality is comorbidity, comorbidity of addiction with mental illness, and comorbidity of addiction with pain. And those are more challenging than when they are in isolation.

Senator SHAHEEN. So did you want to add anything to that?

Dr. COLLINS. I think Dr. Volkow very accurately characterizes the situation.

I think one of the things that we are most concerned about in terms of this crisis, just if I can show you this graph, is the way in which the epidemic, in terms of the overdose deaths, has shifted from being prescription opioids to now fentanyl just going straight off the chart as it gets into the heroin supply. And as more individuals who have fallen into addiction cannot find sufficient access to prescriptions, then they shift over.

EBOLA

Senator SHAHEEN. Absolutely. That is what we are seeing in New Hampshire where we have the highest rate of overdose deaths from fentanyl.

Dr. Fauci, Senator Blunt mentioned the Ebola epidemic and the news report this morning that said the first case had been found in an urban area, a large city, in the Democratic Republic of Congo. And given DRC's other challenges, how worried are we that that epidemic is going to get out of control again?

Dr. FAUCI. Given our prior experience, we are on very high alert about this Ebola outbreak. There are some factors that mitigate against their having the same situation as we saw in West Africa, but there are also factors that actually might favor that. As you mentioned, the first cases that were reported in very early May, the first week in May, were in a place called Bikoro, which is on a remote area called Lake Tumba. The bad news is that it is very difficult to get help in. The good news is it is very difficult to get anybody out.

But what you heard this morning in the report is that there are multiple different zones. Bikoro is one zone. Another zone is

Mbandaka, which is an area that has a city of 1.1 million people. And even though there is only one case there, there is a total now of 44 cases. Even though only two have been confirmed, there are 20 that are probable and 20 that are suspicious. So there are probably many more cases.

What we are doing now is shipping in with the WHO (World Health Organization) helping, obviously, the kinds of things that were the fruits of the work that we did with the support of this committee and others to develop countermeasures. And I will very briefly give you an example.

You heard probably on the media that the WHO has authorized the shipping of the VSV vaccine that had its first phase one trial right at the Clinical Center at the NIH, and then we did it in Africa and that was the one that did the ring vaccination.

We also have ZMapp, which is that triple combination of antibodies that we published in the New England Journal of Medicine from the intramural program at NIH that went over there in Liberia. That is also being shipped.

And we have some experimental drugs, one we are partnering with Gilead, and some monoclonal antibodies that have been developed by the Vaccine Research Center.

So although in direct answer to your question, we are on high alert. We are always concerned when there is Ebola. But we right now have a number of countermeasures that we are able to develop to go in and hopefully block that. So our hopes are—our expectations are always cautious, but the hopes are that we will not have the kind of outbreak that we saw in West Africa.

Senator SHAHEEN. Thank you,

Thank you, Mr. Chairman.

Senator BLUNT. Senator Durbin.

Senator DURBIN. Thanks, Mr. Chairman.

Let me say at the outset that in a world of frustration and partisanship, what is happening in this room this morning is a welcome exception. You will find more positive feelings, more achievement I hope, and more bipartisanship than in almost any other room on Capitol Hill. And I want to salute the chairman of the subcommittee, Senator Blunt, his ranking member, Senator Murray. I told her I was going to praise her before she left. And certainly Senator Alexander in his work and Senator Shaheen. This is a great assignment because with the help of the folks sitting at this table, we actually feel like we are taking steps forward.

And to Senator Blunt for his leadership on this, we have established a standard I think and I hope it is one that we can live by of sustainable, reliable increases in medical research funding in the United States of America. Dr. Collins told me several years ago that is what we need, and we are doing our best to meet that need.

CRISPR

One of the areas that I have recently learned a little bit about was in "Foreign Affairs" magazine of all places, and I happened to be reading it. And this liberal arts lawyer came to try to understand something called CRISPR, which is included in your publication here of promising technologies.

And ironically—I talked to Dr. Collins about this earlier—a family from Illinois came to see me last week, and the mother, the wife, has myotonic dystrophy, and it is a genetic disease which she has unwittingly passed on to her children, a son and daughter, whose circumstances are even more challenging than her own, and of course, their future is really unknown. I mentioned CRISPR to them, and they lit up. They said this is the one area where we feel like there is a chance.

Please, Dr. Collins or one of your colleagues here, give us a moment about CRISPR and what we are doing.

Dr. COLLINS. I am happy to because I agree that this is one of the most exciting things that has happened in a long time in terms of providing tools both for basic science and for therapeutic applications. It opens up entirely new vistas particularly for individuals with genetic disorders where we know there is a misspelling in the DNA. This provides an opportunity to go and fix that in a very precise fashion.

So it is also a great story about basic science because this particular enzyme called Cas9 was discovered in a very obscure area of people trying to understand how bacteria can fight off their own viruses. Bacteria have their own viruses and somehow they manage to survive. And it is a very elegant system where the bacteria have an enzyme that basically recognizes a foreign DNA sequence and goes and snips it and inactivates it. But it is programmable.

And so Jennifer Doudna and her colleagues and Feng Zhang and his colleagues and a few other people who are arguing about who gets the credit basically came up with a way to take that bacterial system and make it work in all kinds of cells, including human cells.

It is very precise. You program it. It can find in a 3 billion letter instruction book—that is our DNA genome—the one that you want to alter and zero in on it and very precisely make a cut or make a substitution.

Now, of course, in the basic science lab, this is fantastic. Every laboratory that is doing molecular biology is using CRISPR Cas9, including mine, including all the people at this table who have active laboratories. But therapeutically the promise here is what I think has us particularly excited.

As I mentioned to you earlier, sickle cell disease may well be the first success of this because for sickle cell disease, the problem is in the bone marrow stem cells. You can take them out. You can purify them. You can utilize this enzyme system to fix the sickle mutation and then put them back. And that should be not just a treatment but a cure for people with this disease, 100,000 of them in the U.S. I think that is going to happen in the next 5 years. The first clinical trials are probably going to start this year.

VAPING

Senator DURBIN. I hate to interrupt you because this is important. I have one other topic I want to mention. And I hope that this subcommittee can zero in on the CRISPR technology and what is happening there. I think there is so much promise.

But I wanted to mention one other thing that is important to most of us. 27 percent of the high school students in the State of

Illinois have something in common. 27 percent of them are now using e-cigarettes and vaping. It used to be 28 percent using tobacco cigarettes. Now they are into e-cigarettes and vaping. And the people who are peddling these products that they inhale with nicotine are putting them in candy flavors. Here is one. The brand is Lung Candy and the flavoring is Cake Batter. In this listing here—it is a long listing of flavors for children to see opportunities for vaping. We see exactly what is happening.

Can I get a comment from any of you about what you consider to be the perils or danger of this type of addiction?

Dr. COLLINS. Dr. Volkow.

Dr. VOLKOW. Indeed, we are very concerned because one of the issues why 50 percent of teenagers say that they are starting to vape only with flavors, 30 percent of them are starting to vape with nicotine and are becoming addicted to nicotine.

And in studies that have been already published, it has been shown that if you start to vape, you are much more likely to then go into nicotine vaping, and then if you got into nicotine vaping, then to go into smoking tobacco. So a major concern is that we will be losing a lot of the advances that we did on prevention of smoking among teenagers.

Another aspect that people do not really recognize is that nicotine acts as a priming. So anything that you take when you have nicotine on board becomes much more reinforcing. And as a result of that, if you get exposed to drugs while you are having nicotine on board, you are much more likely to become addicted. So the concern is not only that these teenagers will become cigarette smokers, as the data has already shown—the risk goes up—but also by doing this, their brain becomes primed to the addictiveness of other substances.

Senator DURBIN. Thank you.

Thanks, Mr. Chairman.

ZIKA

Senator BLUNT. Thank you, Senator Durbin.

Dr. Fauci, let me give you a couple minutes to talk about two things. First, Zika. I was at St. Louis University during the Zika crisis where they were working on Zika vaccine research and felt like they were coming to conclusions. So are we going to have something available next time? And second, flu, specifically universal flu, or whatever you want to talk about on your research on those two topics.

Dr. FAUCI. Thank you, Mr. Chairman.

First, we will take Zika. As you know, as I reported to this committee on more than one occasion, we have progressed in our vaccine trial from the phase 1 trial that we originally did at the NIH to now deploying a phase 2b trial, 2b being relatively advanced to not only ask is it safe, but does it induce the kind of response that you would predict would be effective.

And I am pleased to report to you that today we have ongoing a phase 2b trial in several countries in South America, in Mexico, in the Caribbean, Puerto Rico, in Texas, and in Florida to determine if the vaccine is safe and if it does induce that response. It is scheduled to have between 2,400 and 5,000 people in the study.

We are recruiting very rapidly. We anticipate—and I am pretty cautiously optimistic about that—that we will have it fully accrued by the end of 2018. And then if in fact there is an outbreak, we could get an efficacy signal.

And if there is not, then we are working very closely with the FDA (Food and Drug Administration) if we can get enough of what we call immunogenicity data—namely, it shows that it does induce the kind of response that you want—and bridge that to the animal data, which are very convincing that this is a vaccine that can induce a good response—we are working with the FDA to determine if in fact we can get an accelerated approval. You never anticipate what their decision will be, but they are being very cooperative.

UNIVERSAL FLU VACCINE

Next, universal flu vaccine. Again, we are very grateful to the committee for supporting the addition of the \$40 million in the 2018 omnibus for a universal influenza vaccine. So let me report where we are with that.

We had a meeting in Rockville in June of 2017 in which we developed, in association with experts from all over the world and in the United States in influenza, what we call a strategic plan and a research agenda, which we published in the *Journal of Infectious Diseases* in February of this year.

We are now implementing that plan both from a basic science standpoint but also with candidates that are at various stages of development, namely either preclinical in animal study or a phase 1 or phase 2.

And I might just close by saying you may have read just a couple of days ago an NIAID-sponsored phase 2 trial with the universal flu vaccine candidate in association with the company BiondVax has been initiated. And we started a few months ago one of the trials from our vaccine Research Center.

So things are on track. Obviously, as I mentioned to this committee, it is not going to be an overnight type of a thing, but we are well on the road at various iterations of going towards a universal flu vaccine.

Senator BLUNT. And do you see a point, if we got there—I am assuming what we are trying to get is for every year we would not have to try to calculate what that year's flu was like and, more often than not, be slightly off target.

Dr. FAUCI. You are absolutely correct, Mr. Chairman.

The perfect—and that is going to be difficult to do. A universal flu vaccine would be one that would cover all versions of seasonal and any potential pandemic. But the road we are taking now is to go step by step. I tend to refer to it as universal flu vaccine 1.0, which means that we will not have to worry about any H3. The H3N2 that we do each year and we have to change it a little from season to season, which is the reason why we need to get vaccinated every year, the first version will cover all of the H3N2's. The next one will cover very likely an H1N1. There are two major groups of influenza viruses that have multiple viruses in each group. Getting one that covers both groups is getting close to the perfect one.

So the answer is the end game is that you and I, but most likely our children, will be able to get a vaccine early on in life, a boost, and then maybe every 10 years or so and not have to worry about each year guessing what the next iteration is going to be. It is the guess that is the problem because sometimes you do not get it right, and even when you do, it changes enough that it evades the vaccine. And that is what we are trying to avoid.

Senator BLUNT. Well, I may have unlimited time here, and I may exceed that. Who knows what may happen?

[Laughter.]

FUTURE OF CANCER RESEARCH

Senator BLUNT. Dr. Sharpless, so I think in the United States today there are 15.5 million cancer survivors. In 1971, there were 3 million cancer survivors. An incredibly exciting time. Immunotherapy, the BRAIN Initiative, and, that I assume will have a significant cancer-looking element to it, CRISPR.

You and I have some time here. Could you take just a few minutes, a couple of minutes maybe, and talk about your vision of what you hope and believe can happen over the next handful of years in the Cancer Institute based on what we see happening already?

Dr. SHARPLESS. Sure. I think you are really right about that. It is a very exciting time in cancer research. I recently had a colleague email me. It is like I picked the perfect time to lead the National Cancer Institute because there are all these exciting things going on. In fact, today is the release of the ASCO abstracts. It is sort of like Christmas in our field where all the new advances come out and a number of exciting advances in a variety of different cancers.

So I think there really are a lot of opportunities that cash in on this observation that cancer is not only one disease or 10 diseases but hundreds or thousands of diseases, and each one of them needs its own specific treatment.

So the good news is there is a lot of excitement going on. There are a lot of new technologies and new approaches, and a lot of that research has been empowered by the funding from this committee.

But I think the bad news about it is that problem is somewhat different from what we used to imagine. So we used to think of cancer is like one disease and we had the cardiology paradigm where we put 800 people on one arm of the trial and 800 people on the other arm of the trial. That sort of clinical trials framework no longer really works. So the modern approach to cancer I think has to be somewhat different.

So the things I thought the NCI should focus on are training the workforce so that we have the right kinds of cancer researchers. So we need cancer biologists who really understand basic immunology because it is excessive immunotherapy, and we need cancer researchers who understand big data because we are aggregating data at such a furious pace to try and use that information to treat cancer patients.

We need to recommit to basic science. You know, it is not enough to make progress against some cancers. We really have to make

progress against all cancers, and that requires a basic biological understanding of all cancers.

We need to fix the problem of clinical trials. The structure of clinical trials in cancer has led them to become smaller and more fragmented and much more expensive. And so we need to sort of rethink how we do clinical trials. A very interesting development there is the NCI-MATCH Trial, which will be presented this year at meetings about how we sequence patients and identify the mutations in their tumor and then allocate them to therapy based on the genetic driver, the personalized event that makes their cancer relevant.

And then lastly, we really need to get serious in cancer about organizing our data and aggregating it and linking it so that we have the genomic data, the radiology data, the histology data, the clinical information—we have that all available in a way that is safe and secure, available to the research community so we can understand what mutations cause what patient to respond to this drug and why they lived that long and really get a handle on these bins of rare cancers that we have to treat.

GENETICS AND CANCER

Senator BLUNT. I was out at FDA not too long ago. They have put a cancer team together that I know you are aware of that is looking at all they are doing. You know, the thought in that discussion came up that within the foreseeable future, there just may be something that each individual is prescribed that amps up, if you will, whatever their unique fighting capacity needs to be on their unique attack that is likely to happen to them. That is one look.

The other look is—I am not sure how the genetic—the CRISPR effort works there. But it is an incredibly exciting time. Even with immunology, I would think that 5 years ago an observation made in passing would not have been made at all. This is what we are doing. And there I am sure you are going to continue to work on why this does not work on some cancers and what you need to find. It may not be possible ever, but right now—Dr. Collins, do you want to talk about that?

Dr. COLLINS. I appreciate your raising this, why does it not work when it does not work.

And we talked earlier about partnerships, and I wanted to point to this as a very successful public-private partnership called PACT, the Partnership for Advancing Cancer Therapies. Now 12 biotechnology pharmaceutical companies have partnered with NIH to ask that question. What are the biomarkers that actually tell you that immunotherapy is going to work or it is not? Because we have these dramatic success stories. Emily Whitehead, this little girl that had failed to respond to the traditional treatment for leukemia and who was very much near the end, and who with CAR T-cell therapy was not just successfully treated, she was cured. She is 5 years out now. She looks great and wonderful.

But it does not work for solid tumors nearly as well. Why does it not work for pancreatic cancer? Why does it not work for prostate and breast and brain tumors? We need to figure that out, and that is what this partnership aims to do. In this case no concern about, I think, conflict of interest. It is all pre-competitive. It is all out

there in public. So in this case pharma is contributing both expertise and resources but also cash, and it is pretty exciting to see this taking shape under the leadership of Dr. Sharpless and his colleagues.

Dr. SHARPLESS. Yes. I think that is one of the initiatives to really sort of—you know, each of these therapies requires a really detailed understanding of how they work to make them work in everyone. But it is just leaps and bounds. Every day now we are seeing some new area where we have a drug that used to work and we are making it work better for a whole new class of therapies. And so a lot of good stuff going on.

However, I think it is also important to note that we do still have some cancers, some even reasonably common cancers, where we have not made much progress. So glioma, for example, glioblastoma, brain cancer, is still a real problem, and I think that we really as the NCI have to not only focus on the cancers where we are having successes but also perhaps even more so on the ones that have been recalcitrant and refractory to therapy to date. And so that is an important part of our mission as well.

ALZHEIMER'S AND DEMENTIA

Senator BLUNT. I think the area of greatest spending, certainly the quickest growing spending of Federal health dollars would be Alzheimer's and dementia. And Dr. Hodes, if you and maybe Dr. Koroshetz both would talk about what we are finding there. We have made big investments here. You have probably eliminated a lot of things we know do not work. Now, how are we doing on the other end of that and the dementia impact, too, Dr. Koroshetz, when it comes to you on that? And then when you are done, we will go to Senator Hyde-Smith as she settles in here.

Dr. HODES. Thank you.

I first want to thank the committee, Congress for the increased appropriation of resources towards Alzheimer's disease and related dementias. It has had an enormous impact. For example, in 2015, we funded 152 awards supporting research in this area. 2 years later in 2017, that had increased to 442.

And importantly, this is reflected with confidence and excitement that we heard about across the research community seeing the national commitment to sustained resources, a renewed energy on the part of new and early stage investigators. So of all these new awards we have seen, more than a quarter, 27 percent, were to the categories of early stage and new investigators who had not received any NIH major support previously. An even larger number than that, more than a third, 36 percent, had never had any support for Alzheimer's and related dementias research. So we are bringing into the community not just more dollars and opportunities but the energy that comes with new people willing to commit their careers and to bring new disciplines into the field.

This has included an expansion of the number of clinical trials currently supported to over 140. And equally important, using new techniques of looking at gene expression patterns, proteomics, metabolomics, and an amazingly effective consortium, AMP, Accelerating Medicines Partnership, around Alzheimer's disease to bring public and private science, clinical expertise, and financial support

together to fund new discoveries that have identified the so-called wall of targets now—there had been a consensus to find new molecular targets not appreciated before that might lead to entirely new approaches much needed, in addition to the directions we currently take for translation into clinical trials.

So it is an incredible excitement I think you can appreciate. The numbers are only meant to illustrate the intensity of excitement there is now. Sustained funding has now convinced investigators this is an area in which we can make progress, and the pace has increased exponentially.

Senator BLUNT. I think at Washington University they are feeling more and more positive about a blood test. Things like that that would begin to early identify what was happening with amyloids in the brain would be a big step in the right direction. Hopefully, we can go out there together and look at that sometime.

Dr. HODES. Yes.

Senator BLUNT. Dr. Koroshetz.

Dr. KOROSHETZ. Thanks to the wisdom of the Congress for including what we call the Alzheimer Disease-related dementias in this major effort to decrease the public health problem of dementia in our country. Most patients who have dementia are diagnosed with Alzheimer's disease. Especially in the elderly, when one looks at the brain, one more often than not will find multiple different things going on. And one of the two areas that are most common is the finding of what we call Lewy body disease in people who have dementia diagnosed as Alzheimer's. They have Alzheimer's changes but also have the signature of Parkinson disease, which is synuclein aggregates. So understanding the contribution of these synuclein aggregates not just to Alzheimer's dementia but also to the dementia that occurs in Parkinson's patients who have it for a long time is a focus that we have been able to really pursue much more aggressively.

The other area, which is even more common, is the combination of vascular disease in people who are diagnosed with Alzheimer's disease. And this is, I think, incredibly important to understand because we have made strong progress over the last 70 years in decreasing the risk of stroke, which is the most common consequence of vascular disease in the brain, and also incredibly common in people who have dementia diagnosed as Alzheimer's.

So we have been working with the National Institute on Aging on projects to be able to track the health of the cerebrovascular system in the brain and its contribution to dementia with the hope that the things we already know about, if we can be more aggressive about them, may actually prevent people from going on to develop dementia because we can block this contribution of the vascular component.

Senator BLUNT. Exactly.

Senator Hyde-Smith.

Senator HYDE-SMITH. Thank you, Chairman Blunt.

And thank you, Dr. Collins, for testifying today and all of you for testifying today.

EXPANDING CLINICAL TRIALS TO UNDERSERVED AREAS

I have been involved as a volunteer with the American Cancer Society for many, many years in Mississippi. So I have seen first-hand how new treatments and therapies have transformed the prognosis for so many different types of cancers. And I am grateful for the role that you have played, that NIH has played in so many of those discoveries. What you are all doing is so important, and I truly see it changing and saving lives. And I am grateful to you for that.

However, despite these recent innovations in cancer care, my State of Mississippi continues to have one of the highest cancer mortality rates of any State. For many Mississippians, receiving the cutting-edge treatments and participating in a clinical trial would mean traveling hundreds of miles from home to a cancer center in another State, which is not possible for so many of our patients.

But, Dr. Sharpless, how is the National Cancer Institute working to ensure that patients in States like mine, which do not have an NCI-designated cancer center, are able to participate in clinical trials and benefit from the newest discoveries?

Dr. SHARPLESS. Senator, thanks for the question.

I think you raise a really important issue, which is that it is in some ways great news we are making all this progress against cancer and having those new therapies and new approaches, but if we then cannot disseminate them into the broader community and implement those therapies in sort of the real world, then are we helping people to the extent that we could do so?

So the National Cancer Institute is very concerned about how we assure that our advances translate beyond just the NCI-designated cancer centers, which are a great program but there are only 70 of them, and their range is limited.

One program we have to address this is called the National Community Oncology Research Program, or NCORP, which is 50 NCORP sites that then have each several satellite sites. So there are sort of 900 NCORP sites across the country. Between the cancer centers and NCORP, we reach virtually the entire country. And these sites, in addition to being able to do clinical trials, also have catchment areas that have patients that are more likely to be rural patients as opposed to urban patients and more likely to be underserved minorities. So it is a way that we can enroll a demographic that looks more like the United States in general. So it is a great program. We have just decided to expand its scope somewhat. It is successful and we want to build on that.

And it is also important to note that we can do clinical trials in the NCORP program. For example, the NCI MATCH trial enrolled 6,000 patients at 1,100 sites. It was the fastest accruing trial in the history of the National Cancer Institute, and it allowed us to do accrual in the community, which is also a real need in cancer research because 5 percent of adult oncology patients go on clinical trials. That number needs to be higher, and we need to take the trials to them through like the NCORP program. So it is one way that we are working to address this important issue.

ALL OF US PILOT TESTING

Senator HYDE-SMITH. Wonderful, very good.

And also, I am proud that The University of Mississippi Medical Center and the Jackson-Hinds Comprehensive Health Center were both chosen as sites in the All of Us research program in Mississippi. This program, which seeks to enroll 1 million American volunteers, will no doubt lead to important discoveries that will help doctors identify treatments and personalized to patients' lifestyles, individual's environments and genetic biology. Jackson-Hinds was only one of only six community health centers nationwide chosen to help pilot the project beginning in 2016.

Dr. Collins, as the NIH rolls this program out nationwide this year, how have you incorporated lessons learned through the pilot at Jackson-Hinds that participated in this?

Dr. COLLINS. That is a great question. We did spend the last year in a pilot phase of ramping up All of Us, recognizing this is probably one of the most ambitious projects that NIH has ever mounted, and we needed to have great attention paid to the needs of the participants and particularly for their security and privacy. And we also made a commitment that this was going to be a project that was truly national and it would include people who were traditionally not invited to take part. People in community health centers oftentimes have not been so engaged in research. We wanted to reach out. And Jackson-Hinds was in a particularly powerful place to be one of the first ones to try and see how this would go.

I think we have been very encouraged. In the pilot projects for All of Us, we enrolled over 26,000 people. That makes it one of the biggest studies NIH has done in a long time. And that was just the pilot on the way to our million.

And from the community health centers like Jackson-Hinds, we were gratified to hear a lot of interest on the part of people who came there for their medical care in getting engaged in this kind of research and being included. They wanted to be counted too. They wanted the results of this study to be about them and therefore, provide information that they could use.

So I think it has been a wonderful experience. It has been a kind of outreach we have not necessarily tried at quite this scale before. And now, as of May 6th, we have done the full launch, and anybody in the United States can join up, joinallofus.org. That is all you need to know.

Senator HYDE-SMITH. Great. Well, we certainly appreciate it. All of you.

Senator BLUNT. Thank you, Senator Hyde-Smith.
Senator Shaheen.

TYPE 1 DIABETES

Senator SHAHEEN. Thank you, Mr. Chairman.

I came back because I did not want to go home and tell my family that I had this whole panel from NIH in front of me and I did not ask you about the prospects of research into a cure for type 1 diabetes. I have a granddaughter who has type 1. I also co-chair the Diabetes Caucus in the Senate with Senator Collins and know how devastating the potential is in this country if we do not figure

out a cure for this disease. One in three by 2050 will have diabetes, and it is one of the most expensive, if not the most expensive, chronic diseases that we have.

So can you give me an update on where we are with research?

Dr. COLLINS. Senator, I would be happy to and appreciate your leadership in this.

This is another one of these very exciting areas where things are now moving very quickly for both type 1 and for type 2. Much of the excitement surrounds the potential of developing an artificial pancreas that would take care of the production of insulin when the body has failed to do so at the level it needs to. And you already have seen, of course, the FDA approving the very first example of an artificial pancreas in sort of a closed loop where there is a sensor of what the levels of glucose are and then it administers insulin accordingly. But this is just the beginning of what I think is going to be a remarkable series of advances.

Ultimately the whole stem cell area is going to be critical here as well. We have, after much hard work through the work of people like Doug Melton at Harvard, figured out how you can take a skin cell from somebody, convince it to become what you would call pluripotent and then give it the appropriate set of cocktails to convince it to go down the pathway to be a cell that makes insulin. But it is your own cell. And so ultimately in the view of many of us, that is where we are headed, the opportunity to make an artificial pancreas that does not have silicon in. It actually has your cells that have been reprogrammed to make up for what the other cells that should have been doing this were able to do.

On top of that, I think in terms of prevention particularly of type 2 diabetes where we know that this is tightly connected to obesity and insulin resistance, increasingly trying out the efforts to reduce weight and increase exercise are looking very promising over the long term to keep people who are tipping over into diabetes from actually getting there.

A lot of research as well on gestational diabetes and what kind of information we can learn when this seems to happen during pregnancy. What should be the follow-up to that because that clearly indicates a risk for future illness.

So it is a very exciting time. I could go on much longer, but I wanted to reassure you that NIH is deeply in the middle of all this and the progress is quite gratifying.

ARTIFICIAL PANCREAS

Senator SHAHEEN. Well, I appreciate that. And I am excited about some of the new developments. I think we need to think about how we can reverse the incentives in our healthcare system to do more for prevention with type 2 where it really makes a difference. And unfortunately, I think we are not providing the resources that we need there, and in the long term, it is going to cost us more money.

But I wanted to ask a follow-up because one of the things I have heard from the diabetes community is their frustration with how long it has taken the FDA to approve an artificial pancreas and further developments on that. So we are seeing people in the community who are doing what they call bootleg—and that is probably

not a good term—but are basically making their own artificial pancreas and feel like that provides more relief than they are getting currently, given the system that we have and the dependence on insulin and the way that works.

So can you speak to that? Is that something that you have heard about, and are you concerned about what the risk might be from that?

Dr. COLLINS. I do think there are reasons to be very careful about putting in place an artificial pancreas system without being absolutely confident that it has the appropriate safety mechanisms because we all know that an overdose of insulin can put you into a coma and can ultimately lead to death. So this needs to be a system that is really well worked out. So I understand why the FDA, therefore, has to be pretty rigorous in terms of their evaluation of such things.

I do think, though, that in Scott Gottlieb you have an FDA Commissioner who really is dedicated to moving things along as soon as the data makes it possible.

Senator SHAHEEN. Yes, he has said that. I appreciate that.

Dr. COLLINS. We work very closely with FDA under his leadership. And some of the things that we can do in terms of providing that data is a part of that partnership that we are pushing pretty hard right now.

Senator SHAHEEN. Well, thank you. Thank you all very much for the great work that you are doing.

SOCIAL MEDIA AND SOCIALIZATION

Senator BLUNT. Dr. Koroshetz, do you have anybody looking at the socialization challenges of the constant exposure to social media or the screens as something—the impact that that may have on adolescents and others?

Dr. KOROSHETZ. So certainly social media is taking over our country, and the consequences, whether they are pros or cons, are still yet to be determined.

I think at NIH there are a lot of grantees that are actually using social media to advance health research. I think it would probably be the National Institute of Mental Health, which is looking at the effects on adolescents. But Dr. Volkow can mention a really innovative project which will look at this and other exposures on the development of children that she has just recently—well, almost half finished I guess.

Senator BLUNT. I had a 50–50 shot there I thought.

[Laughter.]

Senator BLUNT. And I missed it.

Dr. VOLKOW. For us, it is important because drug taking and experimentation appears in adolescents, and it is a very social behavior. And many times it follows peer pressure. And one of the things that we have actually tried to understand is how the dramatic changes that have happened in the way that teenagers are interacting with one another may be influencing their behaviors, including drug taking.

But most importantly, our brains are very neuroplastic and they are developing during childhood and adolescence to maximize your ability to respond to your environment. So we are interested to

know if you as an adolescent or as a child get exposed massively to the social communication as opposed to the one-to-one, how does that influence the development of the brain.

So in September of 2016, we started a study with many of our partners at the NIH called the ABCD, Adolescent Brain Cognitive Development, where we are aiming to recruit 10,000 children. We have already recruited 9,500, and we will be finishing in September. But to monitor them on the next 10 years to actually do brain imaging, characterize them cognitively, characterize them socially, and measure how exposure to social media ultimately influences the development of the brain. So this is probably the most notable study that we have because it will allow us to understand how this very dramatic change on how people are interacting with one another may influence the brain.

We also have research to understand how social media is used to actually change the perspectives of teenagers with respect to getting exposed to drugs, the likelihood that they will take a drug when they see it in social media. So the vaping device and the electronic cigarettes, to what extent they are being frequently mentioned in social media are influencing the probability that a teenager will use them. And the same thing with marijuana and the same thing with alcohol.

So this is a completely new world for all of us, and we do not actually, as of now, have an understanding about how it is going to influence the human brain and behavior.

Senator BLUNT. Thank you.

Senator Moran.

Senator MORAN. Chairman, thank you. I am glad the meeting is still going. I do not know that you are pleased with my arrival.

[Laughter.]

Senator MORAN. But I am honored to be here. Thank you.

Senator BLUNT. I am always pleased with your arrival.

Senator MORAN. Thank you, Chairman.

BIOMARKERS AND ALZHEIMER'S DISEASE

Dr. Hodes, I am not exactly sure what has been asked and answered, but I want to pursue a couple of concepts that are now developing in regard to Alzheimer's.

We have talked about detection and the efforts to use biomarkers to identify someone who is at risk or has Alzheimer's before they begin showing symptoms. The National Institute on Aging just coordinated to propose a biological construct which looks at the use of measurable changes in the brain to better understand the earliest biological signs that lead to symptoms.

How will this new framework help to drive research forward? Does it represent a new understanding of the beginning of the disease?

Dr. HODES. Thank you.

The importance of being able to identify the changes that accompany Alzheimer's disease and related dementias early, as you have emphasized, is critical where we think that the best opportunity to intervene at an early point and be able to track success or failure of interventions by measuring biomarkers is going to be absolutely critical.

The definition that you refer to is a publication which suggested that for the pathologic definition of Alzheimer's disease, based on plaques, tangles, and neurodegeneration, there is a set of biomarkers that have standardized, would allow us to assess across studies both longitudinal studies and clinical trials, and in doing so, rigorously harmonize the results of multiple efforts, so more quickly understand which biomarkers are best predictive of disease and importantly, predictive of a response to intervention to treatment or not.

So the studies that Senator Blunt referred to at Wash U are among those. Right now, the biomarkers that are most accessible and most widely used are either imaging, which works extremely well but is cumbersome and expensive, or cerebrospinal fluid analyses which works. But the goal of many now is to establish so-called fluid biomarkers that can take the advantage of blood and serum and identify either a single molecule or a pattern of molecules that will allow us to screen many people, more than we currently can through longitudinal studies and through interventions.

Senator MORAN. Doctor, thank you.

RETURN ON INVESTMENT IN BIOMEDICAL RESEARCH

Let me address this question to Dr. Collins. With the leadership of Senator Blunt and others, we have had success in large part, I would say, because you all have made a case for additional resources within each of your institutes in which the public good is demonstrated and the advancements that are being made are sufficient for American people to feel comfortable that progress is happening and that we are on the cusp of developments that will make a difference in their lives.

In the last year since you were here, Dr. Collins, in this setting, what can I tell my constituents that has transpired to reassure them that their tax dollars are being wisely spent? I sometimes head down the track in a town hall meeting explaining that there are things that we should spend no money on, things we should reduce spending on, and there are things we should spend more money on. And by the time I say that sentence, I am wondering what my constituents are thinking about a Senator from their State who is interested in spending more money on anything. Then I use NIH as the example.

And one of the things that we have been able to do in this subcommittee and the Senate is to prioritize our spending. So it is making decisions about where to spend more money, not just always the thing that I think many Kansans might think happens around here, just spending more money on everything.

So, Dr. Collins, give me the town hall description of how successful our spending has been in the year since we last met.

Dr. COLLINS. I love to give that description. Thank you for the opportunity.

One thing that I would say is maybe the most important discovery that happened in the last year is one we do not know about yet because it was a basic science discovery that sort of seemed at the time interesting, but we did not realize until maybe a year or 2 from now just how profound it might be. We talked about

CRISPR Cas earlier. When that was discovered, nobody had it on their list of the big deal from that year.

Another big discovery that probably we could mention for anybody across this table would be something that has just happened in the more therapeutic applications. In my opening statement, I told the story of a little boy who should not be alive who is walking around and hanging on the monkey bars after being diagnosed with spinal muscular atrophy, a fatal disease, and which with gene therapy now appears to have had a dramatic response.

I could say, well, let us talk about drug abuse. Just yesterday, approval by the FDA of lofexidine, the first non-opioid way to help people withdraw from opioids, which is an effort that NIDA and their colleagues had put together with industry.

With cancer, the advances in cancer immunotherapy, which was already pretty good stuff a year ago—oh, my gosh, it has gotten so much more exciting now with the additional advances, as Ned could no doubt tell you.

In terms of neurological diseases and advances in aging, some of the basic science of aging has also had some interesting findings in the last year about the normal process, not just when it goes awry.

And certainly Dr. Fauci would say, well, goodness, where were we a year ago in terms of Zika and Ebola and where are we now when it comes to such things as a vaccine for the flu, a vaccine for HIV, and maybe also ways to deal with that antimicrobial resistance problem, which have come a long way in that last year.

So my town hall speech has already gone on too long, but I think you get the sense there is a long list of things we could point to in just this last year.

And in case anybody thinks, well, that is fine but is it really worth the money, it is also the greatest return on investment of anything that the government spends money on, \$8.38 of return in 5 years from every dollar that you all allocate to NIH because of what happens in terms of its economic impact.

Senator MORAN. You do, Dr. Collins, what I do in my town hall meetings in wrapping up and concluding and then I have another few paragraphs as well.

Dr. COLLINS. Guilty.

Senator MORAN. But you have a great story to tell and I appreciate you reminding us of those successes. Thank you.

Senator BLUNT. Thank you, Dr. Collins and the Institute directors with you today.

ADDITIONAL COMMITTEE QUESTIONS

The record will stay open for 1 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 TO FRANCIS S. COLLINS, M.D., PH.D.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

PERSONALIZED MEDICINE

Question. Dr. Collins, over the past 3 years, this Subcommittee has provided \$650 million in funding for personalized medicine initiatives, including the recently launched “All of Us” program. At the same time, the National Human Genome Research Institute has continued other important genomics research efforts. As the NIH advances the “All of Us” program, which is a large personalized medicine initiative, how are you ensuring that you continue to leverage and support the genomics expertise and facilities currently in place across the country?

Answer. The NIH thanks the Subcommittee for its support of personalized medicine initiatives overall, and for its support of the All of Us Research Program in particular. The field of precision medicine is a major area of growth across the U.S., and the All of Us Research Program will dramatically advance the fields of personalized medicine and precision health through integrating a wide variety of environmental, behavioral, and biological information at an unprecedented scale. The program launched nationally on May 6, 2018, after establishing a major consortium of academic researcher institutions, healthcare provider organizations, technology experts, community partners, and participants. The program leveraged the expertise of the genomics community through the Genomics Working Group of the All of Us Research Program Advisory Panel which issued a report in December 2017.¹ This Working Group included expertise from academia, industry, and NIH, including the National Human Genome Research Institute. The report provides information on the pros and cons of different approaches and options for corresponding implementation plans, and encompasses effective strategies to generate, analyze, and manage genomic data at the scale of All of Us. The program recently issued a funding announcement for Genome Centers to generate genotype and whole genome sequence data from participants’ biosamples. The program anticipates funding up to two Genome Center awards in fiscal year 2018, with analyses to begin this fall with a goal of ramping up to 200,000 genotypes and whole genome sequences annually. This is a scale only feasible because of the outstanding achievements of the U.S. genomics research community. The program has been able to make major advances in its genomics approach not only through the world-class genomics expertise in its consortium and Advisory Panel, but also through the on-going interactions of its senior leadership with the broader community through frequent participation in events and workshops held by organizations across the country, as well as its strong relationships with Institutes and Centers across NIH, including leveraging the expertise within the National Human Genome Research Institute.

OPIOIDS VACCINE

Question. The fiscal year 2019 budget proposes a coordinated strategy with two primary aims to combat the opioid epidemic in our country. One of those aims is to accelerate the development of new, non-addictive pain therapies with the goal of making a wide-range of therapeutics accessible to those who need them as quickly as possible. Can you describe what types of non-addictive pain therapies are currently in the NIH research pipeline, and how quickly can these therapies can be developed and distributed to the market?

Are there any vaccine candidates being considered?

Answer. NIH is particularly excited about the new Helping to End Addiction Long-term (HEAL) Initiative. HEAL will bolster research across NIH in an effort to improve the treatment of chronic pain by (1) exploring biomarkers that predict the transition from acute to chronic pain, (2) identifying new targets for treating chronic pain using neurotechnologies developed through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and the Stimulating Peripheral Activity to Relieve Conditions (SPARC) program, and (3) building the evidence base on the effectiveness of nondrug and integrated pain treatments. In addition, the Initiative will pursue public-private partnerships to develop new non-addictive pain medicines by sharing data on past and present research projects, and matching researchers with a selection of potentially promising but abandoned pharmaceutical industry compounds to explore their effectiveness for the treatment of pain. Finally, NIH will develop a clinical trials network for pain, allowing multiple new and repurposed compounds to be tested for effectiveness simultaneously.

¹Considerations Toward a Comprehensive Genomics Strategy. Available at: https://allofus.nih.gov/sites/default/files/gwg_final_report.pdf.

The Initiative will tap into the expertise of the NIH Pain Consortium,² a trans-NIH consortium made up of NIH institutes that fund pain research. Funded projects are investigating the entire range of therapeutics development- from preclinical safety and efficacy testing and early phase human trials to health services research. Currently, the consortium members are working on developing more effective and less addictive treatments for chronic pain. For example, a study using a molecular imaging technology called x-ray crystallography has revealed the molecular structure of the receptors that mediate drugs' effects; this information is already leading to the development of safer medications to treat pain.

NIH-funded research is developing medications with properties that affect opioid receptors to produce analgesia with reduced risk of addiction and misuse. Some of these exhibit novel properties as a result of their combined activity at different opioid receptors (mu, delta, and kappa). Compounds with combined activity at the mu and delta receptors or at all three receptors can induce strong analgesia without producing tolerance or dependence in animal models. In addition, the discovery of adjunct medications that can be combined with opioids to reduce the needed dose has the potential to result in lower potential for dependence and addiction. Innovative methods are being explored for drug delivery to increase specificity and efficacy and to reduce analgesic side effects, as well as modified formulations to enhance delivery.

NIH supports an initiative called the Blueprint Neurotherapeutics Program for small molecule drug discovery and development. For example, NINDS funds studies through this program that aim to develop non-addictive kappa opioid receptor antagonists for migraine and a safe, non-opioid analgesic that can be taken orally to reduce diabetic nerve pain.

NIDA continues to fund development of anti-opioid vaccines capable of generating an immune response that would prevent opioids from entering the brain, thereby blocking both their euphoric effects and their dangerous respiratory depressant properties. Current projects include:

- Optimization and preclinical testing of a practical heroin-HIV vaccine³
- Preclinical development of vaccines against heroin, oxycodone, hydrocodone, and fentanyl^{4,5,6,7}

Results from preclinical models thus far have shown that these vaccine candidates are capable of producing an immune response that blocks opioid effects.³² While none have yet advanced to clinical trials, the heroin vaccine candidate developed by the Walter Reed Army Institute of Research in collaboration with NIDA has been in-licensed by Opiant Pharmaceuticals for further development.⁸

QUESTIONS SUBMITTED BY SENATOR LAMAR ALEXANDER

FDA ENFORCEMENT ACTIONS

Question. In April 2018, at my request, the Federation of State Medical Boards issued a report on regenerative and stem cell therapy practices. The report included information on the regulatory history of regenerative medicine and recommendations for state medical boards.

The report described how “some clinics . . . are engaged in the provision of treatment modalities that lack evidence . . . or use what have been described as ‘tokens of scientific legitimacy’ to lend credence to treatments offered or the quality of a clinic and its associated professionals.” According to the report, these tokens include “patient or celebrity testimonials and endorsements, clinician affiliations or memberships in academic or professional societies, and registrations in clinical trials, among others.”

Last week, the Food & Drug Administration (FDA) filed two complaints in Federal court seeking permanent injunctions to stop two stem cell clinics from marketing products without FDA approval. The National Institutes of Health runs

²<https://www.painconsortium.nih.gov/About/Members>.

³https://projectreporter.nih.gov/project_info_description.cfm?aid=9110917&icde=39707102&ddparam=&ddvalue=&ddsub=&cr=20&csb=default&cs=ASC&pball=.

⁴https://projectreporter.nih.gov/project_info_description.cfm?aid=9444613&icde=39707102&ddparam=&ddvalue=&ddsub=&cr=11&csb=default&cs=ASC&pball=.

⁵https://projectreporter.nih.gov/project_info_description.cfm?aid=9330137&icde=39707102&ddparam=&ddvalue=&ddsub=&cr=26&csb=default&cs=ASC&pball=.

⁶https://projectreporter.nih.gov/project_info_description.cfm?aid=9461410&icde=39707102.

⁷Olson ME, Janda KD. Vaccines to combat the opioid crisis: Vaccines that prevent opioids and other substances of abuse from entering the brain could effectively treat addiction and abuse. *EMBO Rep.* 2018 Jan;19(1):5–9.

⁸<https://www.opiant.com/pipeline/heroin-vaccine/>.

clinicaltrials.gov and includes a disclaimer that not all studies on the website have been evaluated by the U.S. Federal Government.

What steps can NIH take to make sure patients visiting clinicaltrials.gov are aware of any enforcement or regulatory actions taken by FDA? Is there any other legislative action Congress can take to help NIH address this issue?

Answer. Research participant safety is of utmost importance to NIH. The ClinicalTrials.gov website currently includes information to help potential participants learn more about the potential benefits and risks of participating in a trial and always recommends talking with trusted healthcare professional before starting a trial. NIH is taking several steps to increase transparency and clarify information on clinicaltrials.gov including:

- Adding more prominent disclaimers explaining that listing a study does not mean it has been evaluated by the U.S. Federal Government
- Adding a question about whether the product being tested is under FDA oversight
- Continuing to evaluate and improve other resources to help potential participants identify questions they may want to consider when deciding whether to participate in research and encouraging them to consult with their healthcare provider on such decisions

NIH is committed to continuing to improve these resources to help ensure people understand important issues to consider before participating in a clinical trial and working closely with FDA to determine best strategies for educating the public on FDA activities and providing information on FDA oversight of clinical research.

NIH does not believe additional legislative action is needed at this time. As noted, NIH is committed to working with FDA to identify ways to improve communication about FDA actions, including enforcement or regulatory actions that may be relevant to information on ClinicalTrials.gov.

QUESTIONS SUBMITTED BY SENATOR JAMES LANKFORD

STEM CELLS

Question. As you know, despite years of research and use of tax dollars, there is currently no validated, successful patient treatment from embryonic stem cells. Additionally, alternatives to embryonic stem cell research exist. In 2012, the Nobel Prize in Physiology or Medicine was awarded to two researchers for their discovery of induced pluripotent stem (iPS) cells, which mimic the qualities of embryonic stem cells but do not use embryos in any way. Similarly, NIH has had great success in treating and curing more than 70 diseases using adult stems cells and iPS cells.

Despite that, in 2009, President Obama issued E.O. 13505, which gave HHS and NIH authority to use human stem cells, including embryonic stem cells, in research. E.O. 13505 revoked a previous EO from President Bush that outlined ethical principles for stem cell research.

Because the research has yet to yield positive results, have you considered a plan to stop embryonic stem cell research or limit such research if the cell line is not already included on the NIH Human Embryonic Stem Cell Registry?

Answer. NIH funds a range of stem cell research, using human and non-human adult stem cells, induced pluripotent stem cells (iPSCs), and since 2001, human embryonic stem cells (hESCs). NIH stem cell research must be conducted in accordance with the NIH Guidelines for Human Stem Cell Research, which detail stringent criteria for voluntary informed consent by which the NIH Director determines the eligibility for use of specific hESC lines in NIH-funded research. NIH-funded stem cell research is exploring applications in regenerative medicine, drug screening, and the study of the molecular pathways in biological development and human disease. Projects studying how undifferentiated stem cells become specialized cells with specific functions in the body have produced knowledge that is essential for developing regenerative medicine treatments. For example, NIH-supported researchers have established protocols for development of specific cell type from hESCs: e.g., pancreatic beta cells (which were effective in a mouse type 1 diabetes model), dopaminergic neurons (tested in a mouse Parkinson's model), liver hepatocytes, and cardiomyocytes. NIH-supported researchers are using hESCs to study cells with particular diseases, such as neurons with a Niemann Pick type C1 mutation, which causes a progressive neurological disease. NIH-supported researchers have also used hESCs to develop organoids, including intestine, colon, and kidney, to model organ-specific diseases.

Several investigational cell therapies developed from hESCs are currently in FDA-regulated clinical trials for spinal cord injury, macular degeneration, and type 1 dia-

betes. The first trial using an investigational cell therapy from iPSCs is taking place in Japan for macular degeneration; an NIH intramural investigator also plans to file an IND this year for using a product from human iPSCs for macular degeneration.

One can never be certain where the next cure or treatment will come from, and maximizing researchers' access to diverse tools, methods, and experimental systems is critical for enhancing the likelihood of success in advancing the NIH mission. Therefore NIH will continue to support highly meritorious research with NIH-approved hESCs.

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

BIG DATA

Question. The Committee directed NIH in the fiscal year 2017 omnibus to develop a strategic plan to address these issues, which was recently released. Now that NIH has a plan, what's the timeline for its implementation?

Answer. The NIH Strategic Plan for Data Science⁹ (subsequently referred to as "the Plan") describes NIH's Overarching Goals, Strategic Objectives, and Implementation Tactics for modernizing the NIH-funded biomedical data-resource ecosystem. The Plan was developed by the NIH Scientific Data Council, and reflects input from HHS, scientists, policymakers, scientific and professional societies, the general public, and leadership and staff from NIH and its constituent Institutes and Centers.

NIH is mapping out the Plan's implementation and expects activities will intensify over the next year. Implementation of key areas are already underway, including the NIH Data Commons Pilot and NIH's cloud-marketplace initiative. In addition, targeted training and career development opportunities to enhance the biomedical data science workforce are in preparation, such as data science fellowships. NIH also is in the process of aligning data science-related funding opportunity announcements to help ensure support for databases, knowledgebases, and tools development are addressed in the most efficient and cost-effective way. Other Plan goals, such as developing data standards, are in early discussion and will require additional research, planning, and interaction with the community to determine the scope and context of future guidance.

As NIH moves forward, the Scientific Data Council, a sub-committee of the NIH Steering Committee composed of Institute and Center directors and deputy directors, as well as key NIH subject matter experts, will have an active role in overseeing execution of the Plan. The NIH Chief Data Strategist, currently being recruited, will collaborate closely with the Scientific Data Council, Data Science Policy Council, and other key NIH stakeholders to lead implementation of the NIH Strategic Plan for Data Science. We anticipate that full implementation plans will be in place within the next year, with a majority of Implementation Tactics launched in the same timeframe.

Question. Given the scale of this undertaking, what does NIH see as the biggest potential barriers to achieving the plan's vision?

Answer. During development of the Plan, a number of data science challenges for NIH were characterized (see pages 4–5 of the Plan). Some of the most pressing barriers to achieving the Plan's vision are summarized below:

- The exponential expansion of data quantity and complexity is increasing costs of data infrastructure, storage and management, including data access, integrity, and privacy considerations.
- The siloed nature of the current data ecosystem is a challenge for data integration, standardization, and interoperability. Implementation of FAIR (Findable, Accessible, Interoperable, and Reusable) principles will enhance stewardship by improving the sustainability of data resources supported through NIH investments.
- The funding mechanisms currently used by NIH incentivize tool development and primary analysis of data but are less compatible with data resource maintenance and sharing. A key objective of the Plan is to tailor the funding mechanisms to the desired outcomes for NIH-supported data resources.
- Novel bridges between academic research institutions, NIH, and the technology industry are needed to enhance development and dissemination of efficient and effective data resources and analytical tools. Flexible funding strategies, includ-

⁹ https://datascience.nih.gov/sites/default/files/NIH_Strategic_Plan_for_Data_Science_Final_508.pdf.

ing expanded use of Other Transaction Authority, would assist in building these bridges.

—A new generation of trained biomedical data science experts will be essential to bringing the vision elaborated in the Plan to fruition. However, the discrepancy in pay scales between the technology industry on the one hand and academics and government on the other presents a challenge for recruiting and retaining talent in data science for biomedical research.

As noted in the response to Question 1, NIH is working to overcome these challenges and implementing new programs and initiatives to address these barriers.

Question. Are there cases where researchers are reluctant or face challenges sharing their data, or they delay releasing that data for years until they've published their findings? What do you do in these situations? Do you see an opportunity to revise policy to address this issue?

Answer. The current culture of data sharing is moving towards openness and transparency. Consistent with these efforts, the NIH encourages and expects the sharing of data from supported research through policies and practices. For example, under the NIH Genomic Data Sharing¹⁰ (GDS) Policy, investigators seeking NIH funding for genomics projects are expected to submit a Genomic Data Sharing Plan as part of the application for funding, which includes the data submission and release timeline. NIH recognizes that different types of genomic data undergo different levels of processing, and the expectations for data submission and data release are based on those levels. However, in general, data are released to NIH-designated data repositories for access by other investigators no later than 6 months after the initial data submission begins, or at the time of acceptance of the first publication, whichever occurs first, without restrictions on publication or other dissemination.

In some cases, restrictions or limitations on the data may exist that prevent broadly sharing the data. For example, based on the informed consent provided by the research participants, there may be limits on who may use the data or for what purposes the data may be used. Other restrictions may stem from legal issues or limitations placed on downstream data use by the study populations who participated in the research, for example tribal populations. In some cases, it may not be appropriate for researchers to share genomic data. In such cases, NIH may grant an exception to the typical data sharing expectations and allow for an alternative genomic data sharing plan. An example of an alternative data sharing plan might be the sharing of summary-level information only. Summary-level information is study data that has been aggregated across the study population (as opposed to sharing data at the level of each individual study participant).

NIH recognizes that investigators often do not want to share their data until they have had the opportunity to publish their own findings. However, at the same time, NIH has a strong interest in increasing the impact and rigor of research studies it funds. Therefore, the NIH officially announced in March 2017¹¹ that researchers may cite their interim research products and claim them as products of NIH funding in order to increase the impact and rigor of a research study. Interim research products can be cited anywhere other research products are cited in the NIH grant application. An example of such a product is a preprint publication, which is a complete and public draft of a scientific document that typically has not yet undergone peer review. NIH encourages investigators to use interim research products, such as preprints, to speed dissemination and enhance the rigor of the research.

NIH also has addressed specific data sharing challenges through targeted policy development. For example, the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information¹² promotes broad dissemination of summary-level results from NIH-funded clinical trials by establishing the expectation that researchers will register the trials in and submit the results information to ClinicalTrials.gov. Under this Policy, NIH expects the results information to be submitted no later than 1 year after the trial's primary completion date.

Another example policy is the NIH 2003 Data Sharing Policy, which expects that investigators submitting a research application requesting \$500,000 or more of direct costs in any single year include a plan for sharing their final research data or state why they cannot. In this Policy, NIH expects the timely release and sharing of data to be no later than the acceptance for publication of the main findings from the final dataset. The specific time will be influenced by the nature of the data collected. However, despite guidance on implementation, there is not a structured format for the plans, and policy compliance has been inconsistent.

¹⁰ https://osp.od.nih.gov/wp-content/uploads/NIH_GDS_Policy.pdf.

¹¹ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-050.html>.

¹² <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html>.

The NIH is evaluating its existing data sharing policies with an eye on furthering the current culture of data sharing. From November 2016 to January 2017, NIH sought public comment on how scientific data generated from NIH-funded research should be managed, and to the fullest extent possible, made publicly available through a Request for Information: Strategies for NIH Data Management, Sharing, and Citation.¹³ This public comment solicitation also specifically asked the public for the greatest barriers and challenges associated with data sharing. Input¹⁴ from the public, which included universities, associations, companies, and publishers, noted specific barriers to data sharing, such as establishing a culture of sharing that would appropriately incentivize and encourage data sharing, the need for community-based standards for long-term preservation or sustainability of data, data preparation and submission, and the costs and resources associated with data management and sharing, e.g., data curation, personnel, infrastructure. Suggestions to resolve some of these barriers included providing incentives (e.g., citation of datasets and attribution for sharing data) to help to change the culture of data sharing. Respondents felt that the use of community-based standards, as well as the ability to budget for data management and sharing in NIH funding applications and proposals, would help mitigate some of the resource barriers associated with data management and sharing.

The NIH intends to continue ongoing outreach and community engagement on existing policies and practices to refine the implementation of existing policies and to develop new policies when warranted to achieve the goal of encouraging a culture of data sharing.

Question. Given the scale of investments Congress is making in Alzheimer's disease, the data we are generating may be used to accelerate major scientific breakthroughs. Has NIA looked at its existing data sharing policies to determine how they are working? Do we know what percentage of grant recipients fulfil their data sharing obligations at the end of their projects?

Answer. NIA does not currently keep an overall tally of compliance with data-sharing plans. With that said, a number of NIA initiatives related to Alzheimer's disease (AD) and related dementias have data-sharing plans built in, and in those situations sharing of data is used as a criterion for continued funding from year to year. Major programs that operate under these terms include the Accelerating Medicines Partnership for AD initiative (AMP-AD); the Model Organism Development and Evaluation for Late-Onset AD (MODEL-AD) initiative; and the Alzheimer's Disease Neuroimaging Initiative (ADNI). We are currently exploring the feasibility of and possible mechanisms for tracking compliance more globally across research project grants.

Question. The committee has prioritized a biomedical research ecosystem that is amplified by sustainable, interoperable, accessible, and usable research data, including Alzheimer's research data. How do you ensure that data sharing is prioritized at the start of the NIH grant process? Is there a process to make sure researchers are preparing to share their data from the start? What are the most frequent comments you hear from researchers about why they can't share their data?

Answer. Effective data sharing relies upon appropriate identification, adoption, and crediting of good data management and sharing practices. Thus, NIH encourages data sharing consistent with the FAIR (Findable, Accessible, Interoperable, Reusable) data principles. For example, in order to facilitate access by qualified investigators to genomic data for the study of Alzheimer's disease, NIH funded the creation of The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site¹⁵ (NIAGADS), currently maintained at the University of Pennsylvania. NIAGADS along with other National Institute for Aging (NIA) approved sites make genomic data and associated phenotypic data available to qualified investigators in the scientific community for secondary analysis in accordance with standards established by the NIA and the NIH Genomic Data Sharing (GDS) Policy.

NIH policies on data sharing typically expect that a plan is submitted with a funding application, indicating for example what data will be shared, and how, when, and where it is expected to be shared. These policy expectations suggest that researchers and institutions should be thinking through these issues during the planning phases of their applications.

For example, the implementation of the NIH GDS Policy sets the expectation that applications for funding that propose the generation of large-scale human or non-human genomic data include a Genomic Data Sharing Plan in the Resource Sharing

¹³ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-015.html>.

¹⁴ https://osp.od.nih.gov/wp-content/uploads/Public_Comments_Data_Management_Sharing_Citation.pdf.

¹⁵ <https://www.niagads.org/>.

Plan section of the grant application. Applicants are expected to describe the data type(s) and repository for data deposition. Applicants proposing to generate human data should also provide information addressing data submission and release timelines, Institutional Review Board assurance of the genomic data sharing plan, the appropriate uses of the data, and if appropriate, a request for a data sharing exception, prior to award. Those proposing to generate non-human data also need to address the data submission and release timelines prior to award. The Genomic Data Sharing Plan is approved by the funding NIH Institute or Center. In addition, for the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, applicants proposing to conduct clinical trials must submit a plan for the dissemination of the trial information.

NIH continues to discuss, with public input, the value of data sharing and what information is most helpful to include in a plan for managing and sharing data that ensures shared data are findable, accessible, interoperable, and reusable (the FAIR principles).¹⁶ NIH and the National Science Foundation held a joint workshop on the Value of Data Sharing in October 2017.¹⁷ Some consistent themes included in plans for data management and sharing among various Federal funders include describing the types of data to be shared; what tools may be needed to analyze shared data; what standards apply to the collected data; how, where, and for how long data will be available; and whether any barriers to data sharing exist.

Through responses to the Request for Information: Strategies for NIH Data Management, Sharing, and Citation,¹⁸ the public indicated that barriers to data sharing include the resources and repositories needed to manage and share data, the need for data standards to ensure that data is reusable and reproducible, and incentives. NIH continues to gauge ways to address these barriers in the process of evaluating its existing data sharing policies and practices.

ALZHEIMER'S VACCINE

Question. In 2000, the NIH set aside \$50 million over 5 years to support research on new ways to treat Alzheimer's disease with a special emphasis on the development of a vaccine to prevent the disease. While the first generation of Alzheimer's vaccines were developed shortly thereafter, in 2008 these studies were halted due to patient safety concerns. Can you describe what the NIH has done in recent years—or plans to do in the future—to support development of a vaccine to treat the more than 5 million Americans currently living with Alzheimer's?

With the most recent omnibus funding bill bringing total 2018 funding to \$1.8 billion, does the NIH plan to fund research for an Alzheimer's vaccine in fiscal year 2019?

The Alzheimer's Association has made a commitment to prevent or effectively treat Alzheimer's disease by 2025. We're less than 6 years away from that target, and in spite of continued Congressional increases to the NIH budget, safe and effective treatments are still out of reach. Can you describe the current research being done, and if you believe there are any gaps in research that could be addressed in fiscal year 2019?

Vaccines have been one of the most effective and impactful medicines in history. Is vaccine research a priority for NIH's Alzheimer's research goals, and if not, why?

Answer. Vaccination is one of many treatment modalities currently under study for both prevention and treatment of Alzheimer's disease and related dementias (AD/ADRD). For example, the Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease (API-ADAD) study is exploring "preventive immunotherapy" among members of an extended Colombian family that carries a genetic mutation placing many members at greatly increased risk of developing the disease. Another study, the Dominantly Inherited Alzheimer's Network (DIAN) trial, evaluates the safety, tolerability, and effectiveness of several drugs, including two vaccines, and will determine if they can prevent, delay, or even reverse Alzheimer's disease changes in the brain. NIA also supports a large cooperative agreement to complete preclinical safety and efficacy testing for AV-1959D, a cutting-edge DNA vaccine. DNA vaccines use pieces of DNA from specific pathogenic proteins to stimulate an immune response and offer potential technical and safety advantages over conventional protein/adjuvant vaccines. All of these studies remain important priorities within our AD/ADRD portfolio and will remain active in fiscal year 2019.

With respect to current AD/ADRD research and gaps, NIA has leveraged the extraordinary influx of funding directed at these diseases to build a series of bold and

¹⁶ <https://www.force11.org/group/fairgroup/fairprinciples>.

¹⁷ <https://osp.od.nih.gov/2017/12/18/data-destiny-debrief-nih-nsf-workshop/>.

¹⁸ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-015.html>.

innovative research programs, infrastructure, and new partnerships that are enabling some of the Nation's leading scientists to tackle the problem of AD/ADRD at an unprecedented scale and pace. High-priority research and infrastructure programs that are currently underway include:

- Alzheimer's Clinical Trial Consortium (ACTC), to accelerate and expand trials of AD/ADRD therapies;
- Resilience-AD, a new program bringing together experts from multiple disciplines to understand why some high-risk individuals remain dementia free;
- Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease (M²OVE-AD) Initiative, exploring how metabolic and vascular risk factors such influence brain aging and AD pathology and identifying blood-based markers of the disease;
- Alzheimer's Biomarker Consortium—Down Syndrome (ABC-DS), in which researchers use biomarkers to track disease progression in people with DS, a uniquely vulnerable population at high risk for developing AD;
- The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) project to develop better animal models of late-onset AD;
- Approximately 140 active clinical trials of interventions to prevent, treat, or manage symptoms of AD/ADRD and to enhance caregiver well-being;
- Development of new therapeutics, including some that target molecules other than beta-amyloid; and
- Harnessing the power of big data to identify existing drugs or combinations currently used to treat other conditions that could be effective for the treatment of AD/ADRD.

Gaps continue to exist around development of caregiver support interventions; implementation of a national recruitment strategy that ensures inclusion of diverse populations in AD/ADRD research; understanding gene-environment interactions that increase risk or confer resilience against AD/ADRD; infrastructure development, including big data infrastructure; workforce training across the spectrum of research; and harmonization and distribution of data from large datasets. NIH considers each of these a priority area for fiscal year 2019, and NIA has begun to implement strategies to fill these gaps, with a number of relevant Funding Opportunity Announcements issued or approved in concept by the National Advisory Council on Aging.

NEXT GENERATION RESEARCHERS

Question. Ensuring a strong pipeline of the best and brightest U.S. scientists is of paramount importance. To this end, the Fred Hutchinson Cancer Research Center in Seattle participates in the Coalition for Next Generation Life Science, which seeks to increase transparency of life science career prospects by providing new data and information to help students make informed choices about their science careers. What steps is the NIH taking to ensure young and mid-career investigators remain engaged in academic research?

The National Academies of Sciences, Engineering, and Medicine released a report in April on the next generation of biomedical and behavioral researchers and recommended that NIH increase by five-fold the number of individual research fellowship (F) awards and career development (K) awards available to support postdoctoral researchers. It also recommended that NIH create a Next Generation Researcher Innovation Fund to support innovative pilot projects that seek to improve and accelerate transitions into independent careers. Which of these recommendations or others in the report, do you anticipate NIH adopting or considering?

Answer. NIH is currently assessing the recommendations of the National Academies Next Generation Researchers Initiative (NGRI) committee, convened in early 2017, to study and recommend solutions to any barriers that may extend periods of training, time to independence, or impede sustained success in research. As you noted, a final report titled, "Next Generation of Biomedical and Behavioral Sciences Researchers: Breaking Through" was released in April 2018. As these recommendations are being considered, NIH is also awaiting a related report from a working group of the Advisory Committee to the Director focused on the next generation of researchers, expected in June 2018. NIH expects to incorporate guidance from both groups to prioritize further actions to bolster the careers of early-stage investigators.

Within the NIH Office of the Director, the Office of Extramural Research's Division of Biomedical Research Workforce conducts regular evaluations of outcomes of NIH training and career development programs. These activities help us assess strategies that are successful in promoting continued engagement in academic research. NIH has, and continues to grow, an evidence-base to support positive im-

pacts of individual postdoctoral fellowship (F) awards and individual career development (K) awards on subsequent, sustained research careers. NIH is currently considering how to optimize the benefits and outcomes of these awards for early stage researchers.

NIH appreciates the recommendation to increase the number of F and K awards. NIH will carefully consider the cost to benefit ratio of increasing their numbers as well as other options, such as enhancing stipends, salary, or research support offered with each award, to maximize their impact on successful research careers.

In addition, as we consider the National Academies' and Advisory Committee to the Director Working Group's recommendations, we will work with the NIH Institutes and Centers to consider expansion of other programs that have been particularly successful for early stage investigators, including:

- NIH Director's New Innovator Award Program (DP2), which supports early-stage investigators of exceptional creativity who propose bold and highly innovative new research approaches with the potential to have a major impact on broad, important problems in biomedical and behavioral research.
- The Maximizing Investigators' Research Award (R35) supports early-stage investigators to enhance their ability to take on ambitious scientific projects, spend time on research, and reduce the time spent writing grant applications.
- The NIH Pathway to Independence Award (K99/R00) program to facilitate a timely transition of outstanding postdoctoral researchers to independent, tenure-track, or equivalent faculty positions and help researchers to launch competitive, independent research careers.
- The Director's Early Independence award (DP5), as part of the NIH Common Fund's high-risk high reward initiative, aims to support more bold and innovative research activities with the opportunity for rapid progress. Specifically, this program accelerates the entry of exceptional junior scientists into an independent research career by forgoing the traditional post-doctoral training period. These select investigators have established a record of scientific innovation and research productivity as well as demonstrated unusual leadership, drive, and maturity.
- The High Priority, Short-Term Project/Bridge Awards (R56) supports early-stage investigators by providing limited, interim research support to gather additional data for revised grant applications.

SALARY CAP

Question. The Administration's fiscal year 2019 budget request proposes limiting the percentage of an investigator's salary that can be paid with grant funds at 90 percent of total salary. Like the fiscal year 2018 proposal to cap facilities and administrative costs, limiting salary support is proposed under the guise of identifying "efficiencies." Congress firmly rejected the proposal to cap F&A in the final fiscal year 2018 omnibus because these infrastructure costs are integral to conducting successful research. Perhaps to an even greater degree, researchers who develop ideas, articulate research questions, design studies, and conduct experiments and clinical trials are essential to quality research and the pursuit of life-saving treatments and cures. Would NIH agree that if Federal support for principal investigators' salaries is cut, in addition to resources being redirected from other activities to cover salaries, wouldn't this send a message to those interested in entering academic research that they may not be fully supported?

Answer. Because Federal research funds are limited, reductions in the NIH contributions to the salary of researchers on NIH grants leaves more funds for additional scientists along with the equipment and resources they need to carry out their critically important work. This may also provide funds that may be used to fund additional grants.

NIH is aware of varying degrees of salary support for its funded scientists. In some institutions, scientists are expected to seek external grant funds to support most of their salaries. Other institutions provide most, if not all, of the salary support.

Based on a NIH enumeration study,¹⁹ the NIH supports approximately 313,049 full-time and part-time positions, or the equivalent of 121,465 full-time employed individuals each year. We believe that approximately half of these full-time researchers are affected by the salary cap. Institutions may choose to increase tuition, utilize funds from their endowments, or solicit state level support to absorb some of the

¹⁹ Pool, Lindsay R., et al. "Size and characteristics of the biomedical research workforce associated with U.S. National Institutes of Health extramural grants." *The FASEB Journal* 30.3 (2015): 1023–1036.

costs engendered by the salary cap. Some stakeholders have voiced concern that stringent salary caps may lead to disincentives for certain highly-skilled clinician scientists who may be well-positioned to conduct the kind of science solicited by NIH. The selective pressures on such individuals may lead to a lower number of them willing to engage in NIH-funded research. The NIH is cognizant of these potential effects, but in no way intends for the policies included in the President's Budget to hinder the critically important biomedical research funded by NIH.

NATIONAL ACADEMY OF MEDICINE

Question. According to the 2015 National Academy of Medicine report *Improving Diagnosis in Healthcare*, eliminating diagnostic errors is a “moral, professional, and public health imperative.” Are there steps that NIH can take to invest in basic research on improving diagnosis in medicine, consistent with the findings of the National Academy of Medicine report? Given NIH's disease-specific institute missions, are there structural barriers, either administrative or legislative, that would need to be addressed for successful advancement of basic research by NIH in improving diagnosis in medicine?

Answer. NIH invests in basic research on improving diagnosis in medicine, primarily through the National Library of Medicine (NLM). Of the approximately \$30 million NLM expects to spend on extramural research projects in fiscal year 2018, about 1/3 supports investigator-initiated research projects in clinical/healthcare informatics and data. NLM-funded researchers have examined safety-related issues such as the unintended consequences of physician order entry, data mining of clinical data repositories, and tools for inpatient monitoring using evidence from the electronic health record (EHR). Current NLM research projects which are consistent with the recommendations of the National Academies study are: ways to monitor clinical workflow to detect adverse events, workflow capture to improve trauma resuscitation outcomes, terminology services to make orders consistent and reduce avoidable CT imaging, extraction of typical and atypical disease progression patterns from multi-site EHRs, and patient medical history representation, extraction and inference from EHRs. NLM's intramural research program also emphasizes analysis of large health data sets to enable discoveries that can inform diagnosis. In addition, the intramural research program supports work on health information/data standards and text processing that can improve the consistency of the terminology used in EHRs to support large scale analysis and extract meaning from narrative text, such as clinical notes, to support research on diagnosis. NLM's expanding portfolio of data science research will emphasize needs of precision medicine initiatives and organizations like OHDSI (Observational Health Data Sciences and Informatics) to characterize completeness, assure accuracy, and mitigate bias in large heterogeneous data sets. One challenging area is the need for large data sets of personal health data from individuals for fundamental research. Restrictions and concerns about access, confidentiality, permissions and bias in the data remain a challenge and are important areas for future research.

QUESTIONS SUBMITTED BY SENATOR JACK REED

BIOETHICAL ISSUES

Question. Gene editing research such as the NIH's Somatic Cell Genomic Editing program holds the potential for curing diseases and significantly improving lives; however, we will need to contend with serious bioethical concerns as we continue to make advances in this research. Can you explain how NIH is staying ahead of bioethical issues as the research continues to progress? How is NIH coordinating these efforts with other Federal agencies, both within and outside of HHS?

Answer. Gene editing technologies are powerful tools that enable a broad range of applications, including investigating gene function, developing better animal models to study specific human diseases, and developing new strategies to reduce the spread of malaria and other infectious diseases by vectors such as mosquitoes (through an application called a gene drive). Gene editing technologies are also already being used in clinical trials to potentially treat genetic or acquired diseases, ranging from infectious diseases to cancer.

The bioethical issues associated with gene editing depend on the specific application of the technology, that is, how the gene editing technology is being used and for what purpose. Applications such as somatic gene therapy, human germline modification, and gene drives to eradicate disease all have different bioethical considerations. In many cases, the bioethical concerns raised by these technologies are similar to those first raised at the advent of recombinant DNA technology and human

gene therapy and are well explored and integrated into current oversight structures. For instance, NIH supports gene therapy research, including gene editing approaches, in somatic cells in humans. Somatic cells are not involved in reproduction, so changes in somatic cells are not inherited by subsequent generations. The well-established oversight frameworks and FDA regulatory authority over human gene therapy trials would apply to clinical research involving gene editing. In fact, gene editing applications have already been in the clinic for several years in trials involving different types of technologies targeting such diseases as HIV infection, cancer, and several genetic disorders such as Hemophilia B.

The potential use of gene editing to modify the human germline such that changes would not only affect an individual, but subsequent generations, has been a subject of ethical debate. NIH has participated in multiple activities of the National Academies of Sciences, Engineering, and Medicine (NASEM) focused on issues related to gene editing. The 2017 NASEM report, *Human Genome Editing: Science, Ethics, and Governance*,²⁰ supported basic research and gene therapy in somatic cells but recommended a cautious approach to heritable gene editing in clinical studies.²¹ Given the ongoing concerns in this space, NIH will not fund any use of gene editing technologies in human embryos (NIH Director's statement, April 28, 2015).²² There are also legislative and regulatory prohibitions including the "Dickey-Wicker" amendment attached to the annual appropriations bill for the Department of Health and Human Services, which prohibits the use of NIH funds for "(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research under applicable Federal regulations."

Potential bioethical issues exist for gene drive technology, which allows for the spread of desired traits through populations of organisms at a faster rate than what typically occurs in nature. This approach could potentially provide a means to address environmental or public health problems (e.g., control of invasive species or vector-borne infectious diseases like malaria), but there are potential ethical concerns, especially related to possible effects on the environment. To engage in a robust conversation and to address ethical, scientific, and safety issues, NIH funded in part a 2016 NASEM study²³ on responsible conduct of gene drive research. In a Director's Statement (June 7, 2016), NIH accepted the report, which included support for continuing basic and applied research in gene drives while holding off on release of gene drive modified organisms into the environment at this time.²⁴

As new gene editing technologies come to fruition, NIH continues to be prepared to investigate their ethical, legal, and social implications (ELSI). For example, the National Human Genome Research Institute (NHGRI), has a Congressionally-mandated, 5 percent set-aside in its extramural budget to fund ELSI research. In anticipation of myriad bioethical issues, NHGRI's ELSI portfolio covers research to explore the downstream implications of emerging genomic technologies.

How is NIH coordinating these efforts with other Federal agencies, both within and outside of HHS?

Answer. NIH has been closely engaged with other Federal agencies, both inside and outside of HHS, on bioethical issues associated with gene editing. NIH works closely with the Food and Drug Administration (FDA) on issues related to gene editing through fora such as the NIH/FDA Joint Leadership Council, in which there is a dedicated effort to coordinate gene editing activities.

NIH continues to participate in many NASEM activities, including the ongoing Human Genome Editing Initiative, which involves many components across the U.S. Government and beyond.²⁵ As noted above, NIH also supported a NASEM study on gene drives, which involved other funders including the Defense Advanced Research Projects Agency, the Foundation for the National Institutes of Health, and the Bill & Melinda Gates Foundation. NIH continues to coordinate with these funders to promote the safe and ethical conduct of gene drives research.

NIH also engages in bioethics conversations in international fora, including discussions of the ethics of gene editing at the fourth "Unite to Cure Conference" in April 2018, which was hosted at the Vatican to discuss the bioethics of gene editing

²⁰ <https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance>.

²¹ <https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance>.

²² <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos>.

²³ <http://nas-sites.org/gene-drives/>.

²⁴ <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-national-academy-sciences-report-gene-drives-non-human-organisms>.

²⁵ <http://nationalacademies.org/gene-editing/index.htm>.

and other biotechnologies with physicians, researchers, and religious thought leaders from across the globe. NIH will continue to engage in such discussions, both inside and outside the government, and both domestically and internationally.

QUESTIONS SUBMITTED BY SENATOR CHRISTOPHER MURPHY

CENTER FOR EXCELLENCE IN GENOMIC SCIENCES

Question. As you know, I represent a State that has two significant academic medical research institutions—Yale University and the University of Connecticut. The University of Connecticut, via a collaboration with the Jackson Labs, has in recent years made significant investments in genomics research, a field that Yale has done work in as well. As the technology and tools to do genomics research and screening have become more widespread, more universities like UConn have aspired to compete for Federal funding.

As you know, the largest of such awards at the National Human Genome Research Institute is called the Center for Excellence in Genomic Sciences (CEGS) program. Each 5-year CEGS grant supports a multi-investigator, interdisciplinary team to develop innovative genomic approaches to address a particular biomedical problem and is funded at up to \$1.75 million annually.

The CEGS program was launched back in 2001 with two awards. Additional rounds of awards in subsequent years eventually expanded that number to 10 centers. However, at present there are only 8 CEGS awards active in the U.S. spread among only 7 research institutions. Furthermore, only 20 institutions total have ever received one of these awards in the past 17 years. I understand the importance of institutional knowledge at these universities but am also concerned that the same players may get these awards while other universities, like UConn, are left with little chance to compete for these larger awards.

Do you have any suggestions on how NIH might address this problem?

Answer. The Centers of Excellence in Genomic Science (CEGS) were established in 2001. Three CEGS awards were made that year, including one to Yale University. NHGRI generally makes one to two CEGS awards per year, although in 3 years we made three or four awards. In the 18 years that the program has existed, NHGRI has issued 23 awards, to 20 institutions. The group of 20 institutions that has benefited from the CEGS program is quite geographically and institutionally diverse.

The CEGS program generally makes awards for 5 years, and only eight institutions have renewed for another 5 years. Awards currently in their first 5 years of funding are located at Harvard Medical School, Stanford University, the University of Washington/Altius Institute for Biomedical Sciences, the University of Chicago, the University of California Berkeley, and the University of Pennsylvania. Those in renewals are located at Yale University, the University of Washington/Arizona State University, Tempe, Stanford University, the University of Southern California, Harvard Medical School, Johns Hopkins University, and the Dana Farber Cancer Institute. NIH recognizes the importance of allowing as many different institutions as possible to benefit from such funding, and, as referenced below, institutions in Connecticut have received various awards from NHGRI. As stated in the CEGS Funding Announcement²⁶ “The total length of support for any Center under this program will not exceed 10 years”. This limit was put in place to encourage diversity of funding recipients.

Applications to renew enter the same competitive pool as applications from institutions applying for CEGS funding for the first time, and not all requests to renew are successful. NHGRI encourages all eligible institutions to consider submitting CEGS applications. NHGRI also strongly recommends that applicants contact program staff early in the application development process, to increase their chances of success.

Research institutions interested in receiving grant money for genomics research are not limited to applying to the CEGS program; they may also choose from a range of funding opportunities with varying award sizes provided by NHGRI and other NIH institutes. Outside of the CEGS program, NHGRI in recent years has issued awards comparable in size to a CEGS award to genomics researchers from Yale University, the University of Connecticut, and Jackson Laboratory for Genomic Medicine in Farmington, Connecticut. The total NHGRI dollars going to Yale and the University of Connecticut in each fiscal year 2017 and fiscal year 2018 are ~\$7 million per fiscal year, and at least \$5.6 million will be awarded in fiscal year 2019.

²⁶ <https://grants.nih.gov/grants/guide/pa-files/PAR-16-436.html>.

A few examples of awards to those institutions are listed below. Several smaller awards have also been awarded to Yale University and the University of Connecticut.

- In fiscal year 2018, Brenton Graveley at the University of Connecticut School of Medicine was awarded \$1,815,769 (\$8,624,902 total for fiscal year 2018–fiscal year 2021) for a Genomic Community Resource Award to develop A Comprehensive Functional Map of Human Protein-RNA Interactions.
- In fiscal year 2016, Richard Lifton at Yale University received a renewal of a Center for Mendelian Genomics Award, which is part of NHGRI's largest funding program, the Genome Sequencing program. This award started in 2011; the current 4-year renewal award is co-funded by NHGRI and the National Heart, Lung, and Blood Institute (NHLBI). In fiscal year 2018, NHGRI is contributing \$1,947,043, and will contribute another \$2,425,542 in fiscal year 2019.
- In fiscal year 2017, Charles Lee at the Jackson Laboratory for Genomic Medicine in Farmington, CT, received \$2,868,077 for fiscal year 2017 and \$1,986,604 for fiscal year 2018, for An Integrative Analysis of Structural Variation for the 1000 Genomes Project, which NHGRI has funded since 2013.

Examples of other NHGRI programs (in order from largest to smallest budgets) include the Genome Sequencing Program (GSP), the Genomic Community Resources Program, the Electronic Medical Records and Genomics (eMERGE) program, and general investigator-initiated (R01 and R21) research grants. These programs include geographically diverse grantees pursuing work on both the basic and clinical sides of the research spectrum. Additionally, NHGRI is not the only, or even the largest, funder of genomic research at NIH. The National Institute on Aging (NIA), the National Cancer Institute (NCI), and the National Institute of Mental Health (NIMH) are examples of other institutes that provide funding for this type of research. Some other non-NHGRI programs that offer funding for large scale genome sequencing are the Gabriella Miller Kids First Pediatric Research Program (GMKF) (Common Fund) and the Trans-Omics for Precision Medicine (TOPMed) program (NHLBI). Interested parties may look to these and other institutes/programs as possible sources of funding as well.

NATIONAL INSTITUTE ON OCCUPATIONAL HEALTH AND SAFETY

Question. As you mentioned in your testimony, the administration's budget request proposes to move the National Institute on Occupational Health and Safety (NIOSH), which is currently located in the Centers for Disease Control and Prevention, into the National Institutes of Health. The 2019 budget also proposes a significant reduction in funding for NIOSH activities from \$335 million to \$200 million.

As you know, NIOSH currently has multiple responsibilities in the areas of occupational health, including research, training of occupational health professions and professionals, and implementing research into practice with our Nation's businesses, manufacturers, forestry, and agricultural sectors.

Could you provide a list of NIH's current research or training activities in the field of occupational health and safety, and provide the NIH's underlying statutory authorities that would enable NIH to implement NIOSH's core mission and its activities?

Statutory authority for NIH activities is found in section 301 and title IV of the Public Health Services Act.

Answer. The fiscal year 2019 Budget proposes consolidating certain HHS research programs into three new institutes within the NIH. The Budget provides \$380 million for the activities of the Agency for Healthcare Research and Quality (AHRQ), which would be renamed the National Institute for Research on Safety and Quality. The National Institute for Occupational Safety and Health (NIOSH), including the Energy Employees Occupational Illness Program (EEOCIPA), currently administered by the Centers for Disease Control and Prevention, and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR), currently administered by the Administration for Community Living, are also proposed for consolidation into the NIH.

NIH currently does not track its research or training activities in the field of occupational health and safety but could do so in the event of a consolidation. The Budget proposal assumes that existing statutory authorities for NIOSH's core mission and activities would be amended to make them available to NIH along with the necessary funding.

Consolidating targeted research programs from across HHS—AHRQ/NIRSQ, NIOSH, NIDILRR—into NIH allows high priority research programs to benefit from focused resources and NIH research infrastructure. NIH will continue to implement strategies to increase operational efficiencies and administrative reforms.

CLINICAL TRIALS DEFINITION

Question. NIH has expanded the definition of clinical trials through a set of case studies to include both fundamental basic and health-related research, which will have a significant impact on and consequences for principal investigators and research projects. Although there were a number of revisions in response to concerns from research universities and associations, issues remain unresolved. Congress included language in the fiscal year 2018 Omnibus to suspend NIH's new definition of clinical trials and called on NIH to revamp the policy with input from the scientific community. With that in mind, could you answer the following questions:

What steps has NIH taken to satisfy the requirement in the fiscal year 2018 Omnibus bill that directs NIH to consult with the basic science research community about the implementation of the new clinical trials definition?

Has NIH considered creating a new or alternative framework to ClinicalTrials.gov for reporting basic science research involving human subjects?

The new clinical trials definition will include small-scale mechanistically driven clinical studies involving human subjects. These studies cannot inform a change in clinical practice, and yet the new definition will impose tremendous costs associated with registration, training, continuing education, record keeping, and special reports under the assumption that these are clinical trials. Is NIH concerned that the new policy will provide a disincentive for this type of research with human subjects?

Answer. As the largest public funder of clinical trials in the United States, currently investing more than \$3 billion each year, the National Institutes of Health (NIH) takes its stewardship of the nation's clinical trial enterprise very seriously. Therefore, NIH must ensure that supported trials investigate a mission-relevant question that is of high priority, do not needlessly duplicate previously conducted trials (in contrast to providing needed replication), and have the highest likelihood to advance knowledge and improve health. To achieve this goal, several challenges in the design, efficiency, and reporting of clinical trials need to be addressed. In combination, these targeted reforms are intended to ensure stewardship and transparency in the scientific enterprise. The NIH definition of a clinical trial, is focused on fostering this stewardship and transparency to assure the public that scientists will report the results of research with human participants—in a timely manner—regardless of how different scientists might classify them.

NIH recognizes the concerns expressed by the research community and has spent the past few years continuing to solicit input and work with the community to chart the best path forward for achieving the aims outlined in NIH's stewardship reforms. Moreover, NIH has taken several steps to satisfy the requirement in the fiscal year 2018 Omnibus bill that directs NIH to consult with the basic science research community regarding its policy on the Dissemination of NIH-Funded Clinical Trial Information.²⁷ For example, NIH leadership met with interested stakeholders on May 2 to discuss their concerns, and NIH leadership met with Senate and House staff to review those discussions and propose plans, including:

- Issuing a Guide Notice stating that for basic science trials that meet the October 2014 NIH definition of a clinical trial NIH will delay enforcement of the NIH policy²⁸ on registration and reporting posted in the Federal Register on September 16, 2016.
- Issuing a Guide Notice describing flexible, lenient implementation of other clinical stewardship and transparency policies as they apply to basic science studies that meet the October 2014 NIH definition of a clinical trial.²⁹
- Issuing a basic science parent Funding Opportunity Announcement (FOA) in early fiscal year 2019 for fundamental human studies that meet the NIH definition of clinical trials. This enables the agency to combine the transparency we all agree on with the recognition that these types of studies often occur outside of the clinic.
- Issuing a targeted Request for Information (RFI) to consult with researchers and the public to determine the reporting standards best suited to fundamental research with human participants. NIH is also interested in soliciting comments to consider alternative frameworks for reporting basic science research involving human subjects.

As stated in the policy issued on September 16, 2016,³⁰ NIH recognizes that additional effort is required to register and report the results of research studies. None-

²⁷ <https://Federalregister.gov/d/2016-22379>.

²⁸ <https://www.Federalregister.gov/documents/2016/09/21/2016-22379/nih-policy-on-the-dissemination-of-nih-funded-clinical-trial-information>.

²⁹ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>.

³⁰ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html>.

theless, reporting the results of scientific work is integral to the scientific method. The benefits of timely registration and reporting will, in the long run, accrue to the investigators as well as to the public, patients, and the enterprise because transparency will improve future research designs and maximize the public's investment—and their trust—in research. Equally important, it will help investigators fulfill the ethical obligation they have to research participants, namely to ensure that the findings from their participation contribute to generalizable knowledge and the advancement of public health.

PULMONARY FIBROSIS

Question. Unfortunately, like many Americans, my family was touched by pulmonary fibrosis years ago when my uncle passed away from this devastating disease. Estimates are that about 200,000 people are affected in the United States, there are 50,000 new cases each year, and 40,000 people die from the disease each year.

In this era of precision medicine, is the NIH and the National Heart, Lung and Blood Institute applying precision medicine approaches to tackling this disease? How can patient registry's, such as the registry created by the Pulmonary Fibrosis Foundation, play a role in NIH precision medicine efforts relating to this group of diseases?

Answer. Pulmonary fibrosis, which causes progressive scarring of lung tissue, can run in families, but the exact cause of the disease is not well understood. The National Heart, Lung, and Blood Institute (NHLBI) supports a vigorous research program on pulmonary fibrosis to improve understanding of the disease and identify better treatments. In 2014, a NHLBI workshop report, "Future Directions in Idiopathic Pulmonary Fibrosis" recommended continued support for precision medicine efforts including genomic and molecular studies.³¹ Examples of NHLBI efforts include:

- NHLBI-funded researchers have used whole-exome sequencing—scanning all of the protein-coding genes in the genome—to better understand genetic factors involved in idiopathic pulmonary fibrosis (IPF). They analyzed data from >250 patients who had pulmonary fibrosis with little or no family history, and found that variation in three genes (TERT, RTEL1 and PARN) is associated with a risk of IPF.³² All three genes had previously been implicated in familial PF and are involved in the maintenance of telomeres (a region at the end of chromosomes that protects the ends chromosome from damage). Shorter telomere length also has been associated with higher mortality in three IPF patient cohorts.³³
- The NHLBI-funded IPF Clinical Research Network (IPFnet) conducted a trial to investigate whether the antioxidant N-Acetylcysteine, when used in combination with immunosuppressant drugs, is effective in patients with IPF. Analysis of the trial results, combined with genetic data from the participants, showed that N-acetylcysteine monotherapy improved clinical outcomes in patients who carry a particular mutation in the Toll-interacting protein (TOLLIP) gene.³⁴
- Genomic and molecular studies have revealed small bits of RNA, called microRNAs, as a potential form of therapy. MicroRNA-29 appears to play a key role in preventing fibrosis in the lung. Researchers at Yale are collaborating with industry to create a similar—but more stable—version of microRNA-29 that can potentially be used as a therapy for IPF. Their current efforts to develop such a therapy have shown promise in mouse models. The same researchers³⁵ also have identified a 52-gene signature³⁶ in the blood that can be used to develop a risk profile for recently diagnosed IPF patients, which may help identify IPF patients who will benefit most from a given therapy.
- In research funded through NHLBI's LungMAP³⁷ and Lung Repair and Regeneration Consortium, as well as a program project grant,³⁸ researchers performed the first single-cell RNA sequencing analysis of epithelial cells in pulmonary fi-

³¹ <https://www.ncbi.nlm.nih.gov/pubmed/24160862>.

³² <https://www.atsjournals.org/doi/abs/10.1164/rccm.201610-2088OC>.

³³ <https://www.ncbi.nlm.nih.gov/pubmed/24948432>.

³⁴ <https://www.ncbi.nlm.nih.gov/pubmed/26331942>.

³⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9270067.

³⁶ <https://www.ncbi.nlm.nih.gov/pubmed/28942086>.

³⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9062494.

³⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9111936.

brosis.³⁹ This revealed aberrant lung epithelial cells that appear to be in an “indeterminate” state of differentiation (cell fate) not seen in normal lung development. This work also provides sequencing data that can be utilized by other researchers conducting future IPF research.

NHLBI encourages IPF investigators to utilize existing clinical resources, including the Pulmonary Fibrosis Foundation’s patient registry and NHLBI’s lung tissue repository,⁴⁰ when submitting grant applications. By leveraging these longitudinal patient data and biosample repositories, alongside the collection of additional genetic and genomic information, clinical researchers have a greater potential to predict risk, disease progression, and response to therapy—information that is necessary to develop precision medicine approaches to treating IPF.

PSYCHOTIC DISORDERS

Question. Despite advancements for many diseases, I continue to hear from constituents frustrated by the slow pace of development of new medicines to treat psychotic disorders such as schizophrenia. The absence of biomarkers and specific molecular targets, as well as the complexity of the brain, create enormous challenges for drug discovery.

What steps can the National Institute of Mental Health (NIMH) be taking to spur development of innovative therapies to treat these devastating disorders? Is NIMH examining the viability of a public-private partnership to advance discovery of new medicines?

Answer. NIMH supports innovative approaches aimed at improving treatment for individuals living with schizophrenia and other psychotic disorders through research on novel therapeutics, biomarkers to inform therapeutics development and treatment, and services and interventions to optimize existing evidence-based treatments.

NIMH supports early-stage therapeutic discovery and development for the treatment of mental illnesses across the drug development pipeline, including first-in-human and early efficacy trials.⁴¹ The NIMH Drug Discovery and Clinical Therapeutics Program supports research to design and develop novel therapeutics agents for the treatment of mental illnesses and supports the NIH National Cooperative Drug/Discovery/Development Groups (NCDDG) program for the Treatment of Mental Disorders.⁴² The NCDDG encourages public-private partnerships to: accelerate the discovery of pharmacological agents targeting novel molecular processes implicated in the pathophysiology of mental illnesses; facilitate the development and validation of predictive assays for developing novel therapeutics for mental illnesses; support early phase human clinical testing to rapidly assess the safety and efficacy of promising drug candidates; and, facilitate the development and validation of new clinical measures or biomarkers suitable for use in human proof of concept trials of novel therapeutics. As an example, the NIMH Psychoactive Drug Screening Program provides the research community with access to broad screening capabilities in the form of pharmacological and functional assays to stimulate innovative research and development efforts including potential therapeutic agents for the treatment of psychiatric disorders.⁴³ In addition, NIMH supports research on the development and testing of novel drug compounds for their potential to improve cognition in people with schizophrenia. These compounds modulate cholinergic signaling in the brain, which plays an important role in arousal, attention, memory, and motivation. Two of these compounds are at the stage of safety and tolerability testing in human subjects.^{44,45} This line of research aims to ameliorate neurocognitive dysfunction, which is a hallmark of schizophrenia and a significant contributor to disability associated with schizophrenia.

To inform novel therapeutics development, NIMH continues to fund research aimed at identifying biomarkers and charting trajectories of psychotic disorders. Through the NIH Neuroscience Blueprint, which uses state-of-the-science brain imaging technologies to acquire and broadly share data about the structural and functional connectivity of the human brain, NIMH co-funds two NIH Human Connectome Projects (HCP) focused on psychosis. One project examines brain ana-

³⁹ <https://www.ncbi.nlm.nih.gov/pubmed/27942595>.

⁴⁰ <https://www.nhlbi.nih.gov/science/lung-tissue-research-consortium-ltrc>.

⁴¹ <https://www.nimh.nih.gov/research-priorities/therapeutics/index.shtml>.

⁴² <https://www.nimh.nih.gov/about/organization/dnbbs/molecular-cellular-and-genomic-neuroscience-research-branch/drug-discovery-and-clinical-therapeutics-program.shtml>.

⁴³ <https://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2017/the-nimh-psychoactive-drug-screening-program-pdsp.shtml>.

⁴⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9339822&icde=32296266.

⁴⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9140071&icde=32296291.

tomical and functional connectivity in individuals with early psychosis.⁴⁶ The second project tests quantitative models of local and long-range neural mechanisms to understand abnormal visual perception in psychosis.⁴⁷ These projects aim to identify neural correlates of clinical symptoms observed in psychosis and could pave the way for novel treatment development. In addition, NIMH supports the North American Prodrome Longitudinal Study (NAPLS), a nine-site consortium combining brain-based biological and clinical markers to predict the onset of psychosis in vulnerable populations and chart trajectories of mental illness. An improved predictive algorithm and better understanding of biological mechanisms underlying psychosis onset could inform patient stratification for clinical trials of novel preventive treatments.⁴⁸ NIMH also supports the Early Psychosis Intervention Network (EPINET) to create a common database of information gathered during routine clinical encounters to inform effective early psychosis care and accelerate research into psychosis risk factors, biomarkers of psychosis risk and onset, and pre-emptive interventions.⁴⁹

In addition to seeking pathways to novel interventions, NIMH is also committed to improving implementation of current evidence-based practices for the treatment of psychosis. Antipsychotic medications provide substantial benefits to many patients, and consistent medication use is associated with lower rates of relapse and re-hospitalization. Through the Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) program, NIMH supports research to help patients maintain treatment through efforts that improve medication adherence, medication monitoring, and the use of technologies to enhance interventions.^{50,51,52,53,54} In addition, the Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (ALACRITY) Research Centers aims to improve the effectiveness, delivery, and quality of evidence-based services in diverse settings for individuals with serious mental illness, including psychotic disorders.^{55,56,57} Through the Early Psychosis Prediction and Prevention (EP3) initiative, NIMH supports several projects to develop and test interventions to improve cognitive and social skills for persons at clinical high risk for psychotic disorders.^{58,59,60,61} NIMH recently issued a funding opportunity announcement to support a large-scale initiative focused on testing the effectiveness of interventions that target early symptoms associated with clinical high risk for psychosis (i.e., problems in thinking, mood, and social functioning suggestive of a pre-psychosis risk state).⁶²

NIMH will continue to fund research on psychotic disorders to identify and develop the breakthrough treatments of tomorrow, as well as to optimize and implement the effective treatments of today. In pursuit of its mission to transform and understand treatment of mental illnesses, NIMH will continue public-private partnerships through the NCDDG and consider other partnerships that support excellent science and the NIMH mission.

NEUROLOGICAL CONDITIONS

Question. As you may know, the 21st Century Cures Act authorized the CDC to implement a national neurological conditions surveillance system. I worked on this section with Sen. Isakson because despite the fact that estimates indicate that one in six Americans lives with a neurologic condition, many condition-specific figures are severely outdated. For instance, the last national study of prevalence and incidence of Multiple sclerosis was done in 1975 and data on the prevalence of Parkinson's disease is based on a 1985 study.

⁴⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9108511&icde=32296915.

⁴⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9109802&icde=32296932.

⁴⁸ <http://campuspress.yale.edu/napls/>.

⁴⁹ <https://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2015/early-psychosis-intervention-network-epinet-a-learning-healthcare-system-for-early-serious-mental-illness.shtml>.

⁵⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9254370&icde=39687639.

⁵¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9201433&icde=39687639.

⁵² https://projectreporter.nih.gov/project_info_description.cfm?aid=9128708&icde=39687639.

⁵³ https://projectreporter.nih.gov/project_info_description.cfm?aid=9361111&icde=39687639.

⁵⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9201713&icde=39687639.

⁵⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9374695&icde=39592663.

⁵⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9485776&icde=39592663.

⁵⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9486324&icde=39592663.

⁵⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9345577&icde=22682332.

⁵⁹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9304884&icde=22682332.

⁶⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9302540&icde=22682334.

⁶¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9302539&icde=22682335.

⁶² <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-211.html>.

How would a neurological disease registry help provide a foundation for evaluating and understanding aspects of neurological conditions? How could such a surveillance system accelerate neurological research?

Answer. For many neurological diseases, there are no recent, reliable data on the incidence, prevalence, geographical distribution, and demographics in the U.S. population, nor for changes over time. Such information can be useful in several ways. These data are essential to understand the societal burden of neurological disorders, which is an important factor that NIH and the research community must consider in setting research priorities, along with scientific opportunity. Such data are also crucial for designing public health programs. In some cases, these data may provide clues to risk factors and potential environmental influences that more targeted studies may follow up, such as reported differences in geographical distribution in multiple sclerosis and the association of some cases of Parkinson's disease with occupational exposure. Data on frequency of diseases also can demonstrate the effectiveness of research on public health; for example, in stroke, for which we do have good data, there has been a 70 percent decline in the age adjusted death rate, reflecting the cumulative benefits of decades of research.

Although potentially useful, surveillance of neurological disorders presents formidable challenges, especially in a healthcare system that does not have a single central record system. There are hundreds of diseases of the brain and nervous system, many of which are difficult to diagnose correctly. Some disorders, like chronic pain, are among the most common of all diseases, and the many rare genetic diseases collectively have an enormous burden despite being individually rare. Together, neurological diseases affect people of all ages, who may be treated via family physicians, various medical specialties, hospitals, nursing homes, or by self-care. All of this makes tracking very difficult because the optimal strategy is different for different diseases. The 21st Century Cures Act acknowledged the difficulty, noting that the surveillance system may initially address a limited number of neurological diseases.

QUESTIONS SUBMITTED BY SENATOR JOE MANCHIN, III

SUPERFUND SITE

Question. Dr. Collins, as you may know, Minden, West Virginia has been listed as a Superfund site by the EPA since 1984 because the small rural community was contaminated with PCBs by an industrial facility related to coal mining.

I am gravely concerned about the reports stating that cancer rates are significantly higher in Minden than the rest of Fayette County and the rest of the State.

The National Toxicology Program ranks PCBs as "reasonably anticipated to be human carcinogens" and the EPA has classified PCBs as a probable human carcinogen. Both designations indicate that there is substantial likelihood that extended exposure to PCB contaminated sites could result in cancer.

Yet, the EPA has found that PCB exposure from the superfund site is not responsible for these high cancer rates or for a cancer cluster in this small, rural Appalachia town. That is why it is so critical that we conduct additional research to fully understand the potential causal connection between PCB exposure and cancer rates.

Dr. Collins, will you commit to directing the National Toxicology Program at NIH to promptly prioritize further research on PCB exposure and the link to cancer?

Further, will you work with me and the other members of this Committee to ensure that the National Institute of Environmental Health Sciences has the resources needed to conduct this critical research?

Answer. Thank you for your questions, and I appreciate your sharing information about the situation with the Superfund site in Minden, West Virginia. The National Institute of Environmental Health Sciences (NIEHS) is home to the National Toxicology Program (NTP), which is dedicated to testing and evaluating substances in the environment. NIEHS and NTP have a long history of funding research into the health effects associated with exposure to polychlorinated biphenyls (PCBs). NTP has conducted extensive rodent studies with component PCBs to try to understand how these components interact in the body to cause cancer. Other NIEHS investments in this area cover relationships between exposure to PCBs and risks of developmental disorders, immune responses, obesity, metabolic disorders and diabetes, and neurological problems. Given their current and past research activities, NIEHS and NTP are well positioned to advise and share information with other agencies involved in answering scientific questions about PCB exposure levels in affected populations.

Question. In 2017, the America's Health Rankings Report ranked West Virginia 46th in overall health. This low ranking is driven by high obesity rates, high rates of smoking, and high rates of drug related deaths. We're also 48th highest in cancer deaths and 49th highest in the number of West Virginians with diabetes.

West Virginia has, in many ways, been left behind as medical advances have saved lives in other places. In fact, I have heard from West Virginians who want to participate in clinical trials, but are forced to leave the state to do so.

Dr. Collins, what is NIH doing to bridge this gap in health outcomes?

How do you ensure that the medical research that you do benefits people in poor, rural communities?

How can we better expand access to research studies and then to successful treatments to rural Americans, particularly in states like mine where the disease burden is so high?

Answer. NIH recognizes the unique health disparities that rural communities face, and as such, rural health is an important area of research for the agency. Through diverse collaborations and partnerships with communities, academic institutions, and state agencies, NIH supports and conducts rural health research to improve health outcomes and reduce rural health disparities with a special emphasis on populations in poor, rural communities. NIH's rural health research focuses on key areas of concern to you and rural residents and are aimed at addressing health disparities that rural populations in West Virginia and around the U.S. experience.

In fiscal year 2017, NIH supported more than 500 rural health-related grants for approximately \$259 million. NIH is committed to ensuring that there are opportunities for poor rural Americans to access the benefits of research and that research addresses the unique strengths and challenges of rural communities. NIH supports several programs focused on cancer, cardiovascular disease, and other chronic diseases disproportionately affecting rural communities. For example, Screen to Save⁶³ is a colorectal cancer outreach and screening initiative aimed at increasing cancer screening rates for individuals in rural communities, particularly among racial and ethnic minority populations. The Heart Truth Community Action Program⁶⁴ initiative engages and empowers women to learn about risk factors for heart disease and steps they can take to live a heart-healthy life. The Strong Hearts, Healthy Communities⁶⁵ program works to reduce rural disparities in cardiovascular disease through community-based interventions (e.g., nutrition and physical activity classes) in ten underserved, rural towns. NIH's Healthcare for Rural Populations Research Initiative⁶⁶ aims to enhance the resources and infrastructure underlying healthcare access and quality for rural populations, including methods for improving oral health in rural school-based cavity prevention programs.

Recognizing the unique needs of Appalachian communities, NIH supports the Kids SIPsmarter⁶⁷ project, a school-based, behavior and health literacy curriculum aimed at improving sugar-sweetened beverages (SSB) behaviors among middle school students in medically underserved Appalachian counties in southwest Virginia. The program uses a two-way short service message strategy to engage caregivers in SSB role modeling and supporting home SSB environment changes. The primary aim is to assess changes in SSB behaviors among 7th grade students at schools receiving Kids SIPsmarter; evaluate changes in secondary student outcomes such as BMI and quality of life; changes in caregiver outcomes; and maintenance of outcomes. The overall goal is to establish an effective, scalable, and sustainable multi-level strategy to improve SSB behaviors and reduce SSB-related health inequities and chronic conditions in rural Appalachia.

Several West Virginia institutions are also engaged in rural health research, including the West Virginia State Department of Health and Human Resources, West Virginia University, West Virginia School of Osteopathic Medicine, CAMC Health Research Institute, and Marshall University. In one West Virginia-based project for example, NIH supports the West Virginia University Stroke Center of Biomedical Research Excellence (WVU Stroke CoBRE),⁶⁸ a part of the WVU Center for Basic and Translational Stroke Research, which works to identify and treat the known risk factors for stroke among Appalachian populations. Research conducted by the WVU Stroke CoBRE focuses on stroke prediction, causes, prevention, acute treatment and rehabilitation. The Stroke CoBRE also has an intensive mentoring pro-

⁶³ <https://www.cancer.gov/about-nci/organization/crhd/blog/2016/screentosave-launch>.

⁶⁴ <https://www.nhlbi.nih.gov/health/educational/hearttruth/partners/grantees.htm>.

⁶⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9245732&icde=34114853.

⁶⁶ <https://www.nlm.nih.gov/programs/extramural/resource-related.html#healthcare-rural>.

⁶⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9495908&icde=39783928.

⁶⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9313278&icde=39683671.

gram for junior investigators. The WVU Stroke CoBRE recently became a formal part of the StrokeNet clinical trial consortium which will allow the Center to conduct multi-centered clinical trials to enhance its rapid translation of basic research into clinical trials and studies.

The Rural West Virginia Responds to Opioid Injection Epidemics: From Data to Action⁶⁹ project seeks to eliminate the opioid epidemic and associated infectious diseases in West Virginia through collaborations with communities and public health agencies. The project will create an evidence-based roadmap to coordinate and improve screening, prevention, and treatment for HIV and other insular injection drug use-associated diseases; develop and test a novel strategy to rapidly identify the emergence of HIV in rural communities; and deploy and evaluate an integrated service delivery model to enhance delivery of evidence-based services, screening strategies, and treatment.

Continued collaborations and partnerships with scientists and organizations from rural communities, such as many in West Virginia, will contribute to NIH's reach in rural communities and support our work to combat rural health disparities.

INSTITUTIONAL DEVELOPMENT AWARD

Question. The Institutional Development Award (NIH IDeA) program has been critical for West Virginia. It brings NIH funding to help build the medical research programs in underserved states.

West Virginia currently only receives about \$20 million in NIH grant funding, but WVU estimates that the economic benefit of these grants in West Virginia is \$180 million and the IDeA program has been critical for expanding access to medical research in my State.

The IDeA program received \$350 million in the bipartisan fiscal year 2018 Omnibus Appropriations bill, but the budget would cut funding for the National Institute of General Medical Sciences—which houses this program—by more than \$935 million, and this program was not even specifically listed.

I believe that we should continue to strongly support this program.

Dr. Collins, what impact the proposed cuts to NIH funding would have on this important program?

Can you tell me why this program was not specifically listed in the budget and what the recommended fiscal year 2019 funding level is?

Can you please speak to the importance of funding research at a wide variety of institutions, particularly those in rural, underserved states?

Answer. The Budget recognizes that importance of funding the highest priority scientific discoveries while also maintaining fiscal responsibility of Federal resources. The IDeA Program will continue to fulfill its congressional mandate of broadening the geographic distribution of NIH funding for biomedical research and enhancing the competitiveness of investigators at institutions located at eligible states and jurisdictions at the fiscal year 2019 funding level.

Consistent with other NIH Institutes, the fiscal year 2019 National Institute of General Medical Sciences (NIGMS) Congressional Justification only included the total program level. Individual NIGMS program details were not provided, also consistent with other NIH Institute Congressional Justifications.

Prior to the increase of the budget caps and the fiscal year 2018 enacted levels, the fiscal year 2019 President's Budget was built on the fiscal year 2018 Annualized CR level which reduced the NIGMS budget by 2.29 percent. Like the overall NIGMS Program level, the fiscal year 2019 President's Budget for the IDeA Program would be reduced by 2.29 percent from the fiscal year 2018 Annualized CR. When comparing fiscal year 2019 President's Budget over the fiscal year 2018 enacted level, the overall NIGMS total program level and the IDeA program would be reduced by 7.6 percent.

The IDeA Program managed by NIGMS is a long-term interventional capacity-building program targeting states and jurisdictions that have consistently trailed in obtaining significant NIH support. The intent of the program is to transform institutions with infrastructure, human resource, and economic challenges to become more competitive biomedical research enterprises through various distinct but complementary initiatives. Some benefits of the IDeA Program in the eligible states and jurisdictions include:

- Builds active biomedical research environments in IDeA states and improves access to modern, state-of-the-art biomedical research for students, researchers, and the general public.

⁶⁹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9412006&icde=39683671.

- Ensures that states without medical schools have an opportunity to develop research capacity for conducting basic, translational, and clinical research.
- Provides opportunities to address health disparities in medically underserved groups residing in IDeA states.
- Promotes SBIR/STTR programs, technology transfer, entrepreneurship, and public-private partnerships that could lead to the formation of bio-related industries, potentially benefitting the local economy.
- Encourages collaborations and leveraging among IDeA research resource centers to capitalize on each other's unique capabilities to solve complex research questions and encourages consolidation of research resources with complementary technologies to improve efficiency and create economies of scale.
- Enhances the competitiveness of institutions by providing opportunities for talented and highly motivated undergraduate students to participate in research training and pursue research careers in the biomedical sciences.
- Develops best practices, training tools, workflows, databases, and analysis tools that assist clinical and translational researchers to develop and perform clinical and translational protocols to address important questions in multiple areas of biomedical science quickly and efficiently.

Funding research at a wide variety of institutions is extremely important to ensure that a rich diversity of scientific and geographical perspectives is represented and that all available human capital is deployed in the critical work of addressing vital biomedical research questions and pressing health problems. Local investigators are often the best equipped and experienced to conduct research on local health concerns. Further, NIH strongly believes that scientific discoveries can arise anywhere where there are well-trained and determined investigators working in adequately resourced environments. Ensuring that all jurisdictions and institutions across the United States are afforded the opportunity to become active and significant contributors to this country's research agenda increases the likelihood of breakthroughs in science and medicine.

MEDICAL RESEARCH CAN SAVE MONEY—ALZHEIMER'S

Question. I am someone who is very concerned about the Federal debt, but I have always supported strong funding for NIH because it is an investment that saves lives, preserves America's role as a global innovator, and has the potential to save a lot more money in the future if we're able to reduce the costs of treating expensive diseases.

Alzheimer's disease, for example, cost West Virginia's Medicaid program \$394 million in 2017 and this cost is expected to increase as the number of people with the disease increases. The Alzheimer's Association estimates that the cost of caring for people with Alzheimer's and dementia will rise from \$236 billion to \$1.1 trillion in 2050. In short, we can't afford to not invest in medical research.

That is why I share my colleagues concern about the President's budget cuts of more than \$2.2 billion to NIH overall and more than \$1.1 billion to the National Institute on Aging in particular relative to the funding that we included in the fiscal year 2018 Omnibus.

Dr. Hodes, as the Director of the National Institute on Aging, can you please speak to the research that your agency is doing on Alzheimer's disease?

Do you believe that investments in this research now is a fiscally responsible choice given the astronomical costs that our country is likely to face as our Nation ages?

Answer. NIA has leveraged the extraordinary influx of funding directed at Alzheimer's disease and related forms of dementia (AD/ADRD) to build a series of bold and innovative research programs, infrastructure, and new partnerships that are enabling some of the Nation's leading scientists to tackle the problem of AD/ADRD on an unprecedented scale and pace. High-priority research and infrastructure programs that are currently underway include:

- Alzheimer's Clinical Trial Consortium (ACTC), to accelerate and expand trials of AD/ADRD therapies;
- Resilience-AD, a new program bringing together experts from multiple disciplines to understand why some high-risk individuals remain dementia free;
- Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease (M²OVE-AD) Initiative, exploring how metabolic and vascular risk factors such influence brain aging and AD pathology and identifying blood-based markers of the disease;
- Alzheimer's Biomarker Consortium—Down Syndrome (ABC-DS), in which researchers use biomarkers to track disease progression in people with DS, a uniquely vulnerable population at high risk for developing AD;

- The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) project to develop better animal models of late-onset AD;
- Approximately 140 active clinical trials of interventions to prevent, treat, or manage symptoms of AD/ADRD and to enhance caregiver well-being;
- Development of new therapeutics, including some that target molecules other than beta-amyloid; and
- Harnessing the power of big data to identify existing drugs or combinations currently used to treat other conditions that could be effective for the treatment of AD/ADRD.

Other current priorities include development of caregiver support interventions; implementation of a national recruitment strategy that ensures inclusion of diverse populations in AD/ADRD research; understanding gene-environment interactions that increase risk or confer resilience against AD/ADRD; infrastructure development, including big data infrastructure; workforce training across the spectrum of research; and harmonization and distribution of data from large datasets.

The financial costs associated with AD/ADRD to affected families and to society are considerable. Data published by the Alzheimer's Association estimate total payments in 2018 for all individuals with AD/ADRD at \$277 billion, much of which will be paid by Medicare and Medicaid. NIH-funded researchers found that, in the last 5 years of life, total health and long-term care spending for people with dementia was more than \$250,000 per person, greater than costs associated with death from other major chronic diseases. Average out-of-pocket spending for patients with dementia was 81 percent higher than for patients without dementia. Caregiving costs, including loss of wage income due to caregiving responsibilities, are also significant.

NIH-supported researchers estimate that delaying onset of AD for 5 years would result in 41 percent lower prevalence and 40 percent lower cost of AD by 2050. Given these findings, research to ameliorate not only the physical and mental burdens of these diseases but also the economic burden is not only fiscally responsible, it is crucial to the health of our economy.

QUESTIONS SUBMITTED BY SENATOR PATRICK J. LEAHY

Institutional Development Award (IDeA)

Question. The IDeA program, operated by the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health (NIH) has long been a fundamental source of support for institutions that participate in biomedical research. With a focus on health-related research, specifically in rural and medically underserved communities, IDeA is critical in the goal of supporting researchers' work to uncover lifesaving methods to combatting disease. In my home State of Vermont, IDeA awards have contributed to advances in genetic research, new medical technologies, and vaccine and drug developments.

With the help of IDeA awards, the University of Vermont, our State's largest research institution, developed the Vermont Genetics Network, the Vermont Center for Immunology and Infectious Diseases, the Vermont Center for Neuroscience, and the Vermont Center on Behavior and Health. IDeA grants have also expanded the employment of STEM professionals in several other institutions of higher education across the State. These institutes have contributed to some of the world's most groundbreaking medical understanding on how to cure lung and heart disease and on understanding the effect of brain disorders on learning and development.

I am concerned that the administration's proposed cuts to NIH and NIGMS will undoubtedly place pressure on the IDeA program by reducing the amount of grant dollars awarded for institutional biomedical research. This means less opportunities for our Nation's institutions to develop lifesaving treatments to debilitating disease.

What are the benefits of the IDeA program in building capacity in states that might not otherwise receive NIH funding, including a description of not only how this program has benefited not just local communities, but also helped advance the national dialogue on biomedical and translational research?

Answer. The overarching mission of the Institutional Development Award (IDeA) Program is inclusive Biomedical Research Capacity-building—to develop and strengthen biomedical science research programs in States/Jurisdictions of the country that are underrepresented in the NIH portfolio, to enable increased engagement and participation of these states in scientific areas that are supported by NIH, and to promote biomedical research capacity and capabilities in these states that are competitive and sustainable. Benefits of the IDeA program in states/jurisdictions receiving IDeA funding include the following:

- Through targeted professional development efforts, the IDeA Program grows and nurtures the pool of next generation scientific leaders and innovators.

- The IDeA program develops and enhances the research facilities and resources in these states/jurisdictions, thereby enabling investigators to expand their contributions to scientific discovery, innovation, and learning.
- Inclusive and sustainable biomedical workforce development pathways are established and formalized that equip local human resources with the appropriate intellectual and technical scientific skills. Biomedically skilled human capital, in turn, can serve as the nidus or help attract the formation of bio-related industries, potentially benefitting the local economy.
- Through meaningful engagement of the local community, both the scientific research community and the community at-large form important partnerships that begin to address vital and urgent scientific questions and regional health priorities.

Within the past year, some of the important contributions made by investigators and other highlights/impacts emanating from the IDeA Program initiatives include the following:

- Vermont IDeA Network of Biomedical Research Excellence (INBRE)⁷⁰ researchers characterized the processing of a protein in neurons called progranulin, a mechanism that impacts the neuropathology of frontotemporal dementia (FTD), a neurodegenerative disorder characterized by progressive changes in personality, behavior, and/or language. FTD is the second most common cause of early-onset Alzheimer's disease. This finding was published in the scientific journal *Molecular Neurodegeneration*.
- A New Mexico Centers of Biomedical Research Excellence (COBRE)⁷¹ team reported on a collaborative intervention to increase awareness on risk of falls for Zuni Native American community. The innovative collaborative approach can produce dramatic improvements in clinical outcomes, health related quality of life, and reductions in healthcare costs. The Zuni Health Initiative (ZHI), an integrated model of community, family and clinic-based education, life style modification and healthcare will facilitate the translation of validated national guidelines for screening and treatment of chronic disease and reduce health disparities in this high-risk population of Zuni American Indians.
- A report from *Advances in Physiology Education* reported on North Dakota INBRE's impact on undergraduate research at rural primarily undergraduate institutions (PUIs) over a 12-year period. Participation of the PUIs in the ND INBRE generated a more robust research culture at the undergraduate institutions. The number of faculty participating in undergraduate research increased two- to four-fold. The high level of student success (550 participants) is supportive of the concept that undergraduate research (350 posters presented) is a value-added component of the INBRE initiative that will help prime the pipeline for the next generation of health professionals in research, service, and teaching.
- A COBRE team from Vermont carried out research on adverse effects associated with using commercially available cigarettes and explored the effects of reducing potential for addiction in highly vulnerable populations (socioeconomically disadvantaged smokers, individuals with psychiatric conditions). Three manuscripts were published that reported the following: (1) significant positive association between using commercially available high nicotine yield cigarettes and risk of nicotine dependence and continuing to smoke during pregnancy in a nationally representative sample of U.S. women of reproductive age (published in *Preventive Medicine*), (2) reducing the nicotine content of cigarettes significantly reduces the addiction potential of cigarette smoking in adults highly vulnerable to tobacco addiction (smokers with psychiatric disorders or socioeconomic disadvantage) (published in *JAMA Psychiatry*), and (3) dependence severity has no moderating influence on the ability of reduced nicotine content cigarettes to lower the addiction potential of smoking, and minimal effects on relief from craving/withdrawal or smoking topography (published in *Preventive Medicine*).
- INBRE researchers from Alaska reported on the ability of the arctic ground squirrel, a seasonal hibernator, to resist brain damage. Investigating how oxygen glucose deprivation induces tolerance has very important translational im-

⁷⁰The IDeA Network of Biomedical Research Excellence (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.

⁷¹The Centers of Biomedical Research Excellence (COBRE) initiative develops and strengthens institutional biomedical research capabilities in IDeA states through three 5-year phases of infrastructure and faculty development of multidisciplinary research centers focused on a specific biomedical science theme.

- plications in ischemic brain injury in stroke patients (reported in *Journal of Neurochemistry*).
- Investigators supported through the Kentucky INBRE elucidated the role of a Zika capsid (membrane) protein in brain damage and published their results in *Nature*.
 - Shayna Bennett, an alumna of Johnson State College in Vermont, was named an awardee of the 2018 National Science Foundation Graduate Research Fellowship Program (GRFP). The program supports graduate students with high potential to be leaders in STEM research. The program supports NSF's goal of developing a workforce that leads the world in advancing science and engineering research. While Shayna was an undergraduate student at Johnson State College, she was funded by the Vermont INBRE to conduct biomedical research from 2014–2015. The experience influenced her decision to pursue a graduate degree in a STEM research field. She is currently a first-year doctoral student in applied mathematics at the University of California Merced.
 - A report at the Advances in Physiological Education demonstrated how the Kansas INBRE annual symposium, a 10-institute collaboration, improved undergraduate education. The 16-year undertaking has supported 1,000 students. Survey results indicate that students and mentors alike find the symposium to be beneficial and enriching of the student experience, with almost 80 percent of student respondents indicated that their participation in the symposium fostered appreciation of research. The KA-INBRE symposium provides a terrific opportunity for students to gain experience in collecting, preparing, and communicating research in a professional environment.
 - An Arkansas COBRE team published their findings on the effects of radiation on normal tissues and certain age-related diseases vis-a-vis aging stem cells and the ability of tissues to regenerate and repair, drive inflammation, and oxidative stress. The report focused on ABT-263, a molecule initially developed as an anti-cancer therapy drug, which could effectively deplete senescent (aging) cells. The depletion appeared to reduce premature aging of the bone marrow due to irradiation and rejuvenated the function of stem cells in normally aged mice (reported in *Nature Medicine*).
 - Investigators supported through the Louisiana IDeA-Clinical and Translational Research (CTR)⁷² award found that *Mycoplasma genitalium* is an etiologic agent of cervicitis in HIV-infected women, providing a potential mechanism for enhanced HIV transmission to an uninfected partner. *M. genitalium* is an emerging sexually transmitted pathogen implicated in inflammatory syndromes of the female reproductive tract (reported in *Journal of Infectious Disease*).
 - Montana IDeA researchers collaborated on a report on the transmission of a pathogen from animals to humans (zoonotic transmission). This work provides a foundation for transdisciplinary investigation of spillover and synthetic theory on zoonotic transmission (reported in *Nature Reviews Microbiology*).
 - A New Hampshire COBRE team reported on a plant-based nanotechnology that could generate an antitumor immune response. The effect was observed to be systemic and durable, resulting in immune-memory and protection from recurrence (reported in *Nature Nanotechnology*).

TICK-BORNE DISEASES

Question. The spread of tick-borne diseases, such as Lyme disease (Lyme), to humans have been increasing in Vermont and many other northern states. While reports of Lyme in Vermont used to be rare in the early 1990s, it is now common to see over 400 confirmed cases reported in a year. This trend has proven to be true for other northeastern and upper Midwestern States as well, as the number of reported cases of Lyme has tripled and the number of high-risk counties has increased by more than 300 percent since the late 1990s. Ticks, and thus Lyme and other tick-borne diseases, have expanded their geographic range and are now being found in places where there were not seen 20 years ago. It is estimated that 20 percent of the population that live in areas where Lyme is common are unaware that they live in high-risk areas for tick-borne diseases.

Given the ever-growing threat of tick-borne diseases, what efforts are NIH pursuing to better detect or cure tick-borne diseases such as Lyme?

⁷²The IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR) initiative develops network infrastructure and capacity in IDeA-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.

Answer. The National Institute of Allergy and Infectious Diseases (NIAID) maintains a diverse research portfolio on Lyme disease and other tick-borne diseases and encourages development of diagnostics, therapeutics, and vaccines to combat these infections. As part of this effort, NIAID engages in important collaborations with Federal partners, Lyme disease experts, patients, and others as a member of the Department of Health and Human Services Tick-Borne Diseases Working Group created by the 21st Century Cures Act.

NIAID supports basic research on how *Borrelia* species, including *B. burgdorferi* and *B. mayonii*, infect the host, multiply, and ultimately cause Lyme disease. Basic research also is underway for a variety of tick-borne infections such as anaplasmosis, babesiosis, tick-borne encephalitis, and others. Findings of these early-stage studies will help to identify targets for additional diagnostic tests, treatments, and vaccines for these infections. For example, NIAID grantees are using real-time imaging to track the spread of bacteria that cause Lyme disease and to monitor treatment effectiveness in infected mice. NIAID scientists also have developed a novel tick infection model for flaviviruses that could be used to evaluate tools to combat the deadly Powassan and tick-borne encephalitis viruses.

NIAID is committed to discovering better ways to diagnose Lyme disease that would enable more informed treatment decisions. In collaboration with the Centers for Disease Control and Prevention and others, NIAID is working to develop novel diagnostics including next generation molecular tests. NIAID-supported scientists are working to identify biomarkers that could allow for earlier and more rapid diagnosis, accurate indication of disease stage and progression, indications of successful treatment, and ability to distinguish between Lyme and other tick-borne infections. NIAID scientists and extramural researchers recently developed a novel tool, the TBD-Serochip, to help differentiate several tick-borne infections. This test is designed to discriminate between eight major tick-borne pathogens in the United States, including species of *Anaplasma*, *Babesia*, and *Borrelia*.

NIAID also supports Lyme disease prevention research, including efforts to develop effective vaccines. NIAID is funding research exploring the adaptation of a successful canine Lyme disease vaccine for potential use in humans. Other NIAID-supported studies are pursuing vaccine strategies to limit Lyme disease transmission, including oral-bait vaccines targeting wildlife reservoirs of *B. burgdorferi* and efforts to target proteins in tick saliva that are critical for effective transmission of Lyme bacteria.

NIAID is committed to supporting basic, translational, and applied research on tick-borne diseases, including studies on the pathogens, the ticks that transmit them, and their vertebrate hosts. Through ongoing research support, as well as collaborations with Federal and public partners, NIAID will continue to advance the development of vaccines, therapeutics, and diagnostics for Lyme and other tick-borne diseases.

QUESTIONS SUBMITTED TO ANTHONY FAUCI, M.D.

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

COMBATTING ANTIBIOTIC RESISTANT BACTERIA

Question. How has the threat posed by antibiotic resistant bacteria changed since you helped write the National Action Plan a few years back? Is the situation worse, better or unchanged?

Answer. The National Institutes of Health (NIH) continues to prioritize research to address the public health threat of antimicrobial resistance. The National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, plays a lead role in addressing the goals of the National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB), including the development of diagnostics, therapeutics, and vaccines for drug-resistant bacteria. The Progress Report: CARB Years 1 and 2⁷³ outlines NIAID-supported efforts, along with those of Federal CARB partners, toward achieving the goals of the National Action Plan for CARB. While our understanding of antibiotic-resistant bacteria—and how to combat them—has improved since the development of the National Action Plan for CARB, the emergence and re-emergence of drug-resistant bacteria continue to pose a threat to the public health. NIH and its CARB partners are committed to sustaining our critical efforts

⁷³ <https://aspe.hhs.gov/system/files/pdf/258516/ProgressYears1and2CARBNationalActionPlan.pdf>.

to develop countermeasures and strategies to address the ongoing challenge of antibiotic-resistant pathogens.

Question. What is the status of efforts to fund clinical trials to test new antibiotics and diagnostics to quickly identify bacterial pathogens?

Answer. NIAID supports a comprehensive research portfolio on antimicrobial resistance, including clinical trials to test new diagnostics, treatments, and vaccines. NIAID is funding highly meritorious research projects on antimicrobial resistance focused on developing: (1) clinical diagnostics; (2) tools to facilitate discovery of novel therapeutics; and (3) prevention strategies. These awards will build on successes in NIH-supported CARB research, including prior support for more than 35 clinical studies through the NIAID Antibacterial Resistance Leadership Group (ARLG), which oversees clinical research to reduce the public health threat of antibacterial resistance. The ARLG has undertaken studies investigating diagnostic devices, optimized treatment regimens, new drugs, and projects on antimicrobial stewardship. NIAID also supports basic and preclinical research to identify promising antibacterial products that may move into clinical trials. NIAID continues to collaborate with the Biomedical Advanced Research and Development Authority (BARDA) on CARB-X, a unique public-private partnership dedicated to accelerating the development of innovative antibacterial products from target/candidate identification and characterization through Phase 1 clinical trials. NIH also continues to partner with BARDA to support the CARB diagnostic challenge seeking to identify innovative, rapid point-of-need diagnostics to combat the development and spread of drug-resistant bacteria, as well as increase antibiotic stewardship. These efforts are critical to generating a robust pipeline of candidate antibiotics and diagnostics to support clinical testing of promising products against drug-resistant organisms.

Question. Does NIH expect these efforts to help reduce the number of drug-resistant infections and deaths that occur each year, or is that too much to expect?

Answer. The ultimate goals of NIAID-supported research on antimicrobial resistance, ranging from basic research to identify targets for antimicrobial products to applied research and clinical trials to test new diagnostics, treatments, and prevention strategies, are to help reduce the number of drug-resistant infections and deaths and to increase antibiotic stewardship. As one example, NIAID scientists have been using next generation sequencing to study the evolution of community acquired methicillin-resistant *Staphylococcus aureus* (MRSA) strains to help identify how these strains developed and to understand why those strains have become more prevalent. This research, which collected MRSA isolates from patients in many geographic regions, may inform new strategies to limit community acquired MRSA infections throughout the United States. NIAID also has evaluated a new drug to treat *Neisseria gonorrhoeae*, a bacterium that is increasingly resistant to currently used drugs, in clinical trials through the Sexually Transmitted Infections Clinical Trials Group and the Phase 1 Clinical Trial Units for Therapeutics. Based on these early studies, which found the investigational gonorrhea therapeutic to be well-tolerated and effective, the drug will advance to later-stage clinical trials. NIH anticipates that its ongoing CARB research and partnerships across government, as well as new activities enabled by increases to CARB research funding in fiscal year 2018, will continue to support progress against antibiotic-resistant bacterial infections.

UNIVERSAL FLU VACCINE

Question. NIH recently announced the phase 2 clinical trial of a potential universal flu vaccine. How long is that trial expected to last, and does NIAID have other vaccine candidates in the pipeline? If so, when might we see trials for candidates begin?

Answer. The National Institutes of Health (NIH) is prioritizing the development of universal influenza vaccines that would represent a groundbreaking advance in influenza preparedness by allowing for durable protection against multiple influenza strains. The National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, has outlined its research priorities for a universal influenza vaccine in a strategic plan published online on February 28, 2018, by The Journal of Infectious Diseases. As one example of research consistent with the strategic plan, NIAID recently launched a Phase 2 clinical trial of an experimental universal influenza vaccine called M-001. The vaccine, which was developed and produced by BiondVax Pharmaceuticals, is designed to stimulate an immune response against peptide sequences shared among many different influenza strains. The clinical study will be conducted at NIAID-funded Vaccine and Treatment Evaluation Units (VTEUs) and is estimated to be completed in early 2019. The VTEUs also are planning to initiate Phase 1 clinical studies to inform the development of universal influenza vaccines, including a study to evaluate whether the addition of a novel adjuvant to an exist-

ing pre-pandemic H5N1 influenza vaccine can enhance the breadth of the immune response to different influenza strains.

NIAID is studying additional strategies to create a universal influenza vaccine, several of which have advanced to early-stage clinical trials. For example, NIAID Vaccine Research Center scientists have initiated Phase 1/2 studies of a universal influenza vaccine approach that includes an investigational DNA-based vaccine followed by a licensed seasonal influenza vaccine “boost” to improve the potency and durability of seasonal influenza vaccines. NIAID also developed a ferritin nanoparticle-based vaccine approach that showed promise in animal testing and is being evaluated in early-stage clinical trials. In another strategy, NIAID scientists developed a vaccine made from non-infectious virus-like particles (VLPs). This VLP-based vaccine candidate incorporates four subtypes of the viral hemagglutinin protein into one vaccine. This candidate broadly protected against multiple influenza virus subtypes in animal models and may advance to clinical trials in the future. NIAID is supporting a number of preclinical studies to evaluate additional universal influenza vaccine candidates. In addition, NIAID funds basic research to better understand how the immune system responds to influenza infection or vaccination, and efforts to develop new assays and reagents to evaluate the efficacy of novel influenza vaccines.

NIAID will continue to support the development of a robust pipeline of candidate universal influenza vaccines that may advance to evaluation in clinical trials. The availability of a universal influenza vaccine would eliminate the need to update and administer the seasonal influenza vaccine each year and could provide protection against newly emerging influenza strains, including those with pandemic potential. NIAID efforts to achieve this important goal will be facilitated by the generous support of the Congress in providing \$100 million dedicated to research on universal influenza vaccines in NIH’s fiscal year 2018 budget.

OPIOID EPIDEMIC

Question. What share of NIDA’s roughly \$1.4 billion budget for fiscal year 2018 will be devoted to opioid-related efforts, be it prevention, clinical trials or the development of new therapeutics?

Answer. We are unable to provide this information until fiscal year 2018 concludes, but we will provide the information when it becomes available.

Question. When can we expect to see the agency’s strategic plan for the opioids initiative, and will it include specific targets and milestones for what we’re trying to achieve?

Answer. The research plan for the Helping to End Addiction Long-term (HEAL) Initiative⁷⁴ is available online. Setting specific targets and milestones is difficult due to the unpredictable nature of scientific inquiry, so at this time, specific targets are not included. The overall goals of the HEAL Initiative are preventing addiction through enhanced pain management and improving treatment for opioid use disorder.

Question. The fiscal year 2019 budget proposes a coordinated strategy with two primary aims to combat the opioid epidemic in our country. One of those aims is to accelerate the development of new, non-addictive pain therapies with the goal of making a wide-range of therapeutics accessible to those who need them as quickly as possible. Can you describe what types of non-addictive pain therapies are currently in the NIH research pipeline, and how quickly can these therapies can be developed and distributed to the market?

Answer. NIH is particularly excited about the new Helping to End Addiction Long-term (HEAL) Initiative. HEAL will bolster research across NIH in an effort to improve the treatment of chronic pain by (1) exploring biomarkers that predict the transition from acute to chronic pain, (2) identifying new targets for treating chronic pain using neurotechnologies developed through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and the Stimulating Peripheral Activity to Relieve Conditions (SPARC) program, and (3) building the evidence base on the effectiveness of nondrug and integrated pain treatments. In addition, the Initiative will pursue public-private partnerships to develop new non-addictive pain medicines by sharing data on past and present research projects, and matching researchers with a selection of potentially promising but abandoned pharmaceutical industry compounds to explore their effectiveness for the treatment of pain. Finally, NIH will develop a clinical trials network for pain, allowing multiple new and repurposed compounds to be tested for effectiveness simultaneously.

⁷⁴ <https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/heal-initiative-research-plan>.

The Initiative will tap into the expertise of the NIH Pain Consortium,⁷⁵ a trans-NIH consortium made up of NIH institutes that fund pain research. Funded projects are investigating the entire range of therapeutics development- from preclinical safety and efficacy testing and early phase human trials to health services research. Currently, the consortium members are working on developing more effective and less addictive treatments for chronic pain. For example, a study using a molecular imaging technology called x-ray crystallography has revealed the molecular structure of the receptors that mediate drugs' effects; this information is already leading to the development of safer medications to treat pain.

NIH-funded research is developing medications with properties that affect opioid receptors to produce analgesia with reduced risk of addiction and misuse. Some of these exhibit novel properties as a result of their combined activity at different types of opioid receptors (mu, delta, and kappa). Compounds with combined activity at the mu and delta receptors or at all three receptors can induce strong analgesia without producing tolerance or dependence in animal models. In addition, the discovery of adjunct medications that can be combined with opioids to reduce the needed dose has the potential to result in lower potential for dependence and addiction. Innovative methods are being explored for drug delivery to increase specificity and efficacy and to reduce analgesic side effects, as well as modified formulations to enhance delivery.

NIH supports an initiative called the Blueprint Neurotherapeutics Program for small molecule drug discovery and development. For example, NINDS funds studies through this program that aim to develop non-addictive kappa opioid receptor antagonists for migraine and a safe, non-opioid analgesic that can be taken orally to reduce diabetic nerve pain.

It is difficult to estimate the time to market for these various alternatives, but NIH is establishing a Clinical Trial Network to accelerate the development of novel non-addictive chronic pain medications and devices by optimizing analgesic trial design, targeting appropriate patient populations for trials, and engaging research expertise at existing clinical sites.

Question. Are there any vaccine candidates being considered?

Answer. NIDA continues to fund development of anti-opioid vaccines capable of generating an immune response that would prevent opioids from entering the brain, thereby blocking both their euphoric effects and their dangerous respiratory depressant properties. Current projects include:

- Optimization and preclinical testing of a practical heroin-HIV vaccine⁷⁶

- Preclinical development of vaccines against heroin, oxycodone, hydrocodone, and fentanyl^{77,78,79}

Results from preclinical models thus far have shown that these vaccine candidates are capable of producing an immune response that blocks opioid effects.⁸⁰ While none have yet advanced to clinical trials, the heroin vaccine candidate developed by the Walter Reed Army Institute of Research in collaboration with NIDA has been in-licensed by Opiant Pharmaceuticals for further development.⁸¹

Question. The budget emphasizes that the NIH will work with the FDA and pharmaceutical partners to build a public-private partnership to accelerate the development of new non-addictive pain therapies. Can you describe what these partnerships will look like, and how small biopharmaceutical companies who may be working on novel approaches might be able to participate?

Answer. As part of the NIH HEAL Initiative, NIH will pursue public-private partnerships to accelerate the development of non-addictive pain medicines by sharing data on past and present research projects, as well as matching researchers with a selection of potentially promising but abandoned pharmaceutical industry compounds to explore their effectiveness for the treatment of pain. Companies of all sizes can participate in this initiative.

⁷⁵ <https://www.painconsortium.nih.gov/About/Members>.

⁷⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9110917&icde=39707102&ddparam=&ddvalue=&ddsub=&cr=20&csb=default&cs=ASC&pball=.

⁷⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9444613&icde=39707102&ddparam=&ddvalue=&ddsub=&cr=11&csb=default&cs=ASC&pball=.

⁷⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9330137&icde=39707102&ddparam=&ddvalue=&ddsub=&cr=26&csb=default&cs=ASC&pball=.

⁷⁹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9461410&icde=39707102.

⁸⁰ Olson ME, Janda KD. Vaccines to combat the opioid crisis: Vaccines that prevent opioids and other substances of abuse from entering the brain could effectively treat addiction and abuse. *EMBO Rep.* 2018 Jan;19(1):5–9.

⁸¹ <https://www.opiant.com/pipeline/heroin-vaccine/>.

QUESTIONS SUBMITTED TO RICHARD HODES, M.D.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

ALZHEIMER'S VACCINE

Question. Dr. Hodes, vaccines have been one of the most impactful medicines in history. Is there the scientific possibility that a vaccine would work in Alzheimer's? What is the state of the research in this area?

Is NIA planning to fund any vaccination programs in fiscal year 2018?

Answer. Vaccination, a form of immunotherapy, using your body's own immune system to help fight disease, is one of many treatment modalities currently under study for both the prevention and treatment of Alzheimer's disease (AD). While we have every reason to hope that we will see positive results from these studies, our cautious optimism is tempered by the acknowledgement that previous vaccine trials have been largely unsuccessful. For example, in 2002 a trial of AN1792, the first vaccine to target deposition of beta-amyloid, a pathological hallmark of the disease, ended early because dangerous brain inflammation occurred in some patients. More recently, industry-supported clinical trials of passive immunization (i.e., direct transfer of antibodies that attack beta-amyloid) with the monoclonal antibodies bapineuzumab and solanezumab produced disappointing results.

However, these studies were initiated in individuals who were already showing clinical symptoms of the disease, and more recent vaccine studies are targeting at-risk individuals much earlier in the disease course, before symptoms appear. For example, the Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease (API-ADAD) study is exploring "preventive immunotherapy" among members of a large extended family that carries a genetic mutation placing many members at greatly increased risk of developing the disease. Another study, the Dominantly Inherited Alzheimer's Network trial, evaluates the safety, tolerability and effectiveness of several drugs, including two vaccines, and will determine if they can prevent, delay, or even reverse Alzheimer's disease changes in the brain. The Alzheimer's Prevention Initiative APOE4 Trial (API APOE), or Generation 1 study, is determining the safety and efficacy of two drugs targeting beta-amyloid, including an active immunotherapy injection, in older adults at genetic risk of the disease, while the Anti-Amyloid treatment in Asymptomatic AD Trial (A4 Trial) is evaluating a passive vaccine in clinically normal older adults with evidence of AD pathology on screening positron emission tomography imaging who are at risk for developing dementia.

NIA also supports a large cooperative agreement to complete preclinical safety and efficacy testing for AV-1959D, a cutting edge "DNA vaccine." DNA vaccines use pieces of DNA from specific pathogenic proteins to stimulate an immune response and offer potential technical and safety advantages over conventional protein/adjuvant vaccines.

More broadly, NIA supports research on underlying mechanisms of the immune system in the brain. For example, one study is exploring immune-mediated mechanisms underlying clearance of beta-amyloid from the brain and central nervous system, while others are investigating possible immunotherapies targeting tau, another pathological hallmark of AD. All of this important work will be active in fiscal year 2018 and 2019.

TRANS-ANGIOGENESIS

Question. In May 2013, the NIH hosted the NIH Trans-Angiogenesis Workshop. In March 2016, the NIH released a meeting summary, which included an outline of clear steps needed to bring angiogenesis research forward. The resources needed included:

- Develop potential partnerships with pharmaceutical companies for the development of new drugs that require investigations using structural biology approaches and medicinal chemistry.
- Develop cross-disciplinary NIH resources to increase research on the molecular understanding of angiogenesis across therapeutic fields, such as cancer, diabetes, obesity, and cardiovascular diseases.
- Develop a biomarker identification project that moves beyond prognostic biomarkers to the development of validated predictive biomarkers of clinical benefit (or lack of benefit) and biomarkers of toxicity.
- Improve the translation of basic research angiogenesis focused findings across disciplinary fields to clinical applications.

- Organize a cross-disciplinary meeting of basic science, translational and clinical scientists and clinicians where NIH grantees would be required to present their research.
- Create trans-NIH Program Project Grants and Specialized Centers of Clinically Oriented Research for angiogenesis research.

Could you please provide the Subcommittee an update on the progress on these issues?

Answer. Angiogenesis is the process of new blood vessel formation and growth that is vital for normal embryonic development, new blood vessel formation, and wound healing. Insufficient, excessive, or aberrant angiogenesis may have significant clinical consequences in diseases such as stroke, myocardial infarction, peripheral arterial disease, cancer, chronic inflammation, and retinopathy.

Multiple NIH Institutes fund angiogenesis-related research aimed at improving the understanding of normal and abnormal angiogenesis and translating findings into therapeutic interventions.

Because angiogenesis research applies to many diseases, the trans-NIH workshop was convened to provide leaders in angiogenesis research an opportunity to examine the diverse nature of the sciences involved across the field, to identify current gaps, and to explore potential advantages in integrating basic, translational, and clinical research in the prevention and treatment of angiogenesis-related diseases.⁸² NIH has continued to address research gaps and focus on priorities identified by the workshop. Here are a few examples:

BASIC AND TRANSLATIONAL RESEARCH

Research supported by the National Heart, Lung, and Blood Institute (NHLBI) has contributed to a better understanding of angiogenesis mechanisms at the molecular and cellular level.⁸³ Signaling pathways and regulation of angiogenesis have been better defined,⁸⁴ as has the role of inflammation and metabolism of cells that line the interior surface of vessels in angiogenesis.⁸⁵ For example, researchers found that changes in endothelial cell glucose, fatty acid, and protein metabolism may function as a “metabolic switch” for angiogenesis. Further investigation of these pathways is ongoing to identify biomarkers of endothelial cell health and disease and to discover potential ways to alter defective angiogenesis.

Recognizing that cancers need a blood supply to grow and spread, the National Cancer Institute (NCI) provides support for research on elucidating the cellular mechanisms that give rise to the creation of new blood vessels and the therapeutic potential of anti-angiogenesis drugs. One area of particular interest is the action of vascular endothelial growth factor (VEGF) and other signaling molecules that stimulate angiogenesis. Since the discovery of VEGF almost 30 years ago, these proteins have become a major target for therapy; drugs that inhibit VEGF have become an intensively studied—and in some cases, successful—approach to block abnormal angiogenesis.

Yet, some cancers are also resistant to these inhibitors. Researchers are examining the basic mechanisms of resistance in glioblastoma, with a focus on VEGF and stromal-cell derived factor 1 (SDF-1), a protein involved in tumor growth and metastasis.⁸⁶ NCI also supports basic research into tumor microenvironments, which may help illuminate future therapeutic pathways. Examples include a project examining the role of low oxygen, acidity, and depleted nutrient levels in the tumor microenvironment, and the effects these factors may have on glioblastoma angiogenesis,⁸⁷ as well as a study on how immune system activity promotes angiogenesis in melanoma tumor microenvironments.⁸⁸

Angiogenesis research is also relevant to stroke, as collateral blood vessels around a blocked vessel can provide an alternative path for blood flow to the brain. Researchers funded by the National Institute on Neurological Disorders and Stroke (NINDS) are exploring the molecular and genetic mechanisms that determine the number and size of collateral vessels around major arteries, as well as the remodeling of these vessels after a stroke. Researchers also are exploring the role of angiogenic pathways in brain blood vessel stability and the risk for hemorrhage, as well as in processes that support protection and recovery of brain tissue following

⁸² <https://prevention.cancer.gov/news-and-events/meetings-and-events/trans-nih-angiogenesis-workshop/meeting-summary>.

⁸³ <http://circres.ahajournals.org/content/120/11/1713/tab-supplemental>.

⁸⁴ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4966612/>.

⁸⁵ <https://www.ncbi.nlm.nih.gov/pubmed/29795441>.

⁸⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=8997986.

⁸⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9274829.

⁸⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9236367.

a stroke. Additionally, NINDS-funded investigators are exploring avenues to improve the effectiveness of angiogenesis inhibitors for treating brain cancers such as glioblastoma. Ongoing work is investigating the molecular mechanisms that lead to therapeutic resistance, and tumor recurrence and progression.

Angiogenesis research is also important to eye health. Diabetes and the most common type of age-related macular degeneration (AMD) can cause vision loss due to abnormal blood vessels in the retina. Researchers funded by the National Eye Institute (NEI) have demonstrated that gene therapy can be used effectively to block proteins in the VEGF pathway to reduce vision loss in animal models.⁸⁹ This proof of concept supports a novel treatment for angiogenesis-related retinopathy.

CLINICAL RESEARCH

The NCI hopes to expand the successes of angiogenesis inhibitors in treating cancer and currently supports clinical trials of these agents to treat glioblastoma, pancreatic cancer, metastatic breast cancer, prostate cancer, ovarian cancer, colorectal cancer, lung cancer, liver cancer and other solid tumors. Many of these trials involve the therapeutic agent bevacizumab (Avastin), a monoclonal antibody directed against VEGF.

The NHLBI also funds significant clinical research relating to angiogenesis. This includes a planning grant for a clinical trial testing an anti-angiogenesis drug to treat hereditary hemorrhagic telangiectasia, a genetic disorder that involves abnormal blood vessel formation and can result in hemorrhage and stroke.

NHLBI has also supported research to develop pro-angiogenic factors to treat ischemic diseases that restrict blood supply. Such efforts have not yielded reproducible and sustained success in late-stage clinical trials.⁹⁰ While the use of pro-angiogenic stem cells may offer more promise, its clinical application is still limited.⁹¹

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) supports a range of intramural and extramural research projects on aspects of angiogenesis, specifically on development of the utero-placental interface, placenta formation, and early development of the vascular system. In addition to investigator-initiated research, NICHD also supports clinical research aimed at achieving healthier pregnancy outcomes through its Maternal Fetal Medicine Units network. Recently, similarities in the pathology of cardiovascular disease and preeclampsia, a dangerous spike in a pregnant woman's blood pressure, prompted NICHD-supported researchers to conduct a preliminary study of a commonly used cardiovascular drug in high-risk pregnant women in their second trimester. While the risk of preeclampsia was unchanged in women who received a placebo, women who received this drug did not develop preeclampsia.⁹²

A noninvasive retinal imaging approach called optical coherence tomography (OCT) has emerged as an effective tool to view the layers of the retina as well as any fluid leakage—a useful biomarker for AMD and for responses to treatment.⁹³ Over the past decade, the introduction of anti-angiogenesis drugs, such as Avastin, Lucentis, and Eylea has revolutionized treatment of AMD, slowing the disease and even reversing vision loss in some cases. However, monthly treatment injections are expensive and not always needed. OCT is also used for treatment decisions for other angiogenesis-related causes of blindness, such as diabetic retinopathy.

TRANS-NIH EFFORTS

Question. Several NIH Institutes are involved in a Neuroscience Blueprint initiative—Neurobiology of Small Blood and Lymphatic Vessels in Health and Disease. This initiative will support the development of innovative tools and technologies to explore heterogeneity of small blood and lymphatic vessels in the central nervous system (CNS), as well as human studies to identify targets, biomarkers, and mechanisms specific to CNS small blood and lymphatic vessels. This initiative emerged from a trans-NIH scientific workshop on the role of small vessels in health and disease across different organ systems in the body.⁹⁴ While not specifically focused on angiogenesis research, it may support angiogenesis projects.

⁸⁹ <https://www.ncbi.nlm.nih.gov/pubmed/29730824>.

⁹⁰ https://journals.lww.com/cardiovascularpharm/Abstract/2014/08000/Identifying_and_Overcoming_Obstacles_in_Angiogenic.1.aspx.

⁹¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4869986/>.

⁹² <https://www.ncbi.nlm.nih.gov/pubmed/?term=26723196>.

⁹³ <https://www.ncbi.nlm.nih.gov/pubmed/29077605>.

⁹⁴ <https://www.ncbi.nlm.nih.gov/pubmed/27815267>.

Because angiogenesis plays an essential role in health and is implicated in a wide range of diseases and disorders, the NIH will continue to support a full spectrum of research in this area, including development of pro- and anti-angiogenic therapies.

QUESTIONS SUBMITTED TO NORMAN SHARPLESS, M.D.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

CANCER RESEARCH & TREATMENT IN RURAL COMMUNITIES

Question. The network of National Cancer Institute-designated cancer centers and comprehensive cancer centers play an important role in our national efforts to prevent, diagnose, and treat cancer. As someone from a rural state who understands the difficulty in access to cancer treatments in rural and remote areas, Dr. Sharpless, can you describe how existing resources are used to help those Americans in rural and underserved communities?

How do NCI-designated cancer centers ensure those in rural communities can benefit from clinical trials and breakthrough cancer treatments?

Answer. Rural communities face disadvantages compared with urban areas, including higher poverty, lower educational attainment, and lack of access to health services. These challenges contribute to higher incidence of certain cancers and worse cancer-related outcomes in low-income, underserved rural populations. New data has shown that—for the first time—cancer death rates are higher in rural areas than in urban areas. This shift has been demonstrated by two studies—one by NCI researchers⁹⁵ and one led by researchers from the Centers for Disease Control and Prevention (CDC).⁹⁶

There are several areas where the National Cancer Institute (NCI) plays a significant role in advancing rural cancer prevention and control research. Key areas include working with NCI's Community Oncology Research Program (NCORP) and NCI-Designated Cancer Centers to build on their experience with community outreach and developing partnerships with local organizations. To inform NCI's efforts to better address cancer disparities in rural communities, NCI is also convening researchers, community representatives, and providers to discuss these important issues. In May 2018, NCI hosted a diverse group of speakers from across these disciplines to discuss collaboration and coordination for rural cancer control. The objectives of the meeting were to (1) identify gaps in rural cancer research and practice; (2) to build partnerships across the country to address challenges and disseminate solutions; and (3) to highlight and identify methods to address competing and common agendas of clinics/providers, researchers, and community/patients.⁹⁷

NCI has a broad and growing range of research in this area and will continue to work with the cancer community and others to refine and reinvigorate our cancer control efforts in rural areas across the country. NCORP is a crucial part of NCI's efforts to prevent, diagnose, and treat cancer in rural populations.⁹⁸ NCORP's mission is to bring clinical trials and cancer care delivery research to people where they live, with a special focus on rural communities. NCORP is comprised of seven research bases; 46 community sites, 12 of which are designated as minority/underserved;⁹⁹ and more than 900 component sites across the country.¹⁰⁰ NCORP community and component sites, which are comprised of public hospitals, physician practices, academic medical centers, and other groups that provide healthcare services in community settings, play an important role in accruing patients to NCI-supported research studies and clinical trials, including the groundbreaking NCI Molecular Analysis for Therapy Choice (NCI-MATCH) precision medicine cancer treatment trial.

NCI-Designated Cancer Centers also play an increasingly important role in rural cancer control. There are currently 70 NCI-Designated Cancer Centers located in 36 States and the District of Columbia. These cancer centers develop and translate scientific knowledge from promising laboratory discoveries into breakthrough treatments for cancer patients. Each year, approximately 250,000 patients receive their cancer diagnosis at an NCI-Designated Cancer Center, and an even larger number

⁹⁵ <https://www.ncbi.nlm.nih.gov/pubmed/28600296>.

⁹⁶ <https://www.cdc.gov/mmwr/volumes/66/ss/ss6614a1.htm>.

⁹⁷ <https://cancercontrol.cancer.gov/research-emphasis/meetings/arcc-meeting.html>.

⁹⁸ <https://ncorp.cancer.gov/>.

⁹⁹ NCORP minority/underserved sites have a patient population that is of at least 30 percent racial/ethnic minorities or rural residents.

¹⁰⁰ <https://ncorp.cancer.gov/findasite/map.html>.

of patients are treated for cancer and/or enrolled in a clinical trial at these centers.¹⁰¹ Cancer centers applying for NCI-designation are required to describe the geographic area they intend to serve, and are encouraged to describe how the center plans to extend its reach beyond this catchment area to bring the center's expertise to bear on wider populations, including rural populations.¹⁰²

To incentivize cancer center engagement in rural health, NCI has provided supplemental funding to 15 cancer centers to collect additional data concerning their catchment area population and align local measures with national ones, enabling more direct comparisons across centers and with national surveillance data. To extend this commitment, in fiscal year 2018, NCI plans to support NCI-Designated Cancer Centers in further developing their rural cancer control research capacity.

In addition to the programs described above, NCI recently released a standalone Funding Opportunity Announcement (FOA) inviting applications for research aimed at improving the reach and quality of cancer care in rural populations.¹⁰³ Depending on receipt of sufficiently meritorious applications, NCI intends to fund up to 10 awards in fiscal year 2018.

PEDIATRIC CANCER

Question. Dr. Sharpless, we hear a lot about the need for more research on childhood cancer, often from families who have lost a child to cancer. What is the National Cancer Institute doing to improve outcomes for children with cancer, and to address the factors that make childhood cancers unique?

Answer. Pediatric cancer research remains a top priority for the National Cancer Institute (NCI), and each year the Institute identifies the best research opportunities to build upon the foundation of basic science, further develop the scientific understanding of genetic drivers of childhood cancers, identify effective therapies, and enhance the quality of life for pediatric cancer survivors.

NCI recognizes cancers that strike infants, children, teens and even young adults are different from those that affect adults, and that they require specific research. Additionally, even when long-term survival is achieved, many survivors of childhood cancer experience serious long-term adverse effects from the disease or its treatment. Future discoveries made through additional research are needed so that new, more effective, and less toxic treatments for cancers that affect children and young adults can be developed.

Recognizing that childhood cancers are distinct from adult cancers, NCI supports numerous targeted programs aimed at advancing research in pediatric oncology. These efforts include:

- The Children's Oncology Group (COG),¹⁰⁴ part of NCI's National Clinical Trials Network (NCTN), develops and coordinates pediatric clinical trials across more than 200 member institutions. In addition to conducting late-phase clinical trials, the COG receives NCI support for the Phase 1 and Pilot Consortium,¹⁰⁵ which conducts early-phase trials and pilot studies to rapidly introduce new anticancer agents into pediatric care.
- The Pediatric Oncology Branch (POB)¹⁰⁶ in NCI's Center for Cancer Research, part of NCI's intramural research program, conducts high-risk, high-impact basic, translational, and clinical research.
- The NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Trial,¹⁰⁷ launched in July 2017, tests molecularly targeted therapies in children and adolescents with advanced cancers who have few other treatment options. This nationwide trial is open to children and adolescents from 1 to 21 years of age and currently has eight treatment arms.
- Other efforts include the Pediatric Preclinical Testing Consortium (PPTC),¹⁰⁸ the Therapeutically Applicable Research to Generate Effective Treatments (TARGET)¹⁰⁹ program, the NCI Experimental Therapeutics (NExT) Program,¹¹⁰ the Childhood Cancer Survivor Study (CCSS),¹¹¹ the Pediatric Provoc-

¹⁰¹ <https://www.cancer.gov/research/nci-role/cancer-centers>.

¹⁰² <https://grants.nih.gov/grants/guide/pa-files/PA-17-095.html>.

¹⁰³ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-18-026.html>.

¹⁰⁴ <https://www.childrensoncologygroup.org/>.

¹⁰⁵ <https://www.childrensoncologygroup.org/index.php/phase-1-home>.

¹⁰⁶ <https://ccr.cancer.gov/Pediatric-Oncology-Branch>.

¹⁰⁷ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>.

¹⁰⁸ <http://www.ncipptc.org/>.

¹⁰⁹ <https://ocg.cancer.gov/programs/target>.

¹¹⁰ <https://next.cancer.gov/>.

¹¹¹ <https://www.cancer.gov/types/childhood-cancers/ccss>.

ative Questions (PQ) Program,¹¹² the Pediatric Brain Tumor Consortium (PBTC),¹¹³ the Pediatric Cancer Immunotherapy Trials Network (CITN),¹¹⁴ and the New Approaches to Neuroblastoma Therapy (NANT)¹¹⁵ Consortium.

In addition to these well-established programs, the Institute is enthusiastic about the scientific opportunities provided by the Cancer MoonshotSM to stimulate further investigation of pediatric cancers. Current programs supported by the Cancer MoonshotSM include the Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium, which will seek to develop models of, and therapeutic agents for, fusion-driven childhood cancer;¹¹⁶ the Pediatric Immunotherapy Translational Science Network, which will aim to identify targets for immunotherapy treatments for pediatric patients;¹¹⁷ and the Rare Tumor Patient Engagement Network,¹¹⁸ which aims to study rare tumors, including pediatric tumors, and develop a network of clinical trials.

NCI is committed to addressing the unique scientific challenges and opportunities that pediatric cancers pose in ways that lead to better outcomes for children with cancer. NCI continues to demonstrate this commitment through its ongoing support for childhood and adolescent cancer research efforts, through a continued investment in basic research and other crosscutting research efforts, and through its collaborations with the childhood cancer community.

NCI also encourages you to visit the “Childhood Cancers Research” page on its website for additional information about current research, including more comprehensive descriptions of some of the programs mentioned above.¹¹⁹ Research on pediatric cancers will continue to be a top priority.

INDEFINITE DELIVERY/INDEFINITE QUANTITY

Question. It is my understanding that NIH is using more Indefinite Delivery/Indefinite Quantity (ID/IQ) awards, which can provide several advantages: (1) greater competition in the procurement process; (2) smaller well-defined program tasks; (3) tighter financial control on each program task; and (4) incremental milestone driven funding. However, many small, not-for-profit contractors have a difficult time justifying the large commitment of time and resources when contracts are small and delayed. Therefore, the return-on-investment for contractors is becoming harder to justify. Can you discuss the issues NIH faces with ID/IQ contracts and why they are not being more regularly awarded?

Answer. NIH makes regular use of Indefinite Delivery/Indefinite Quantity (ID/IQ) contracts and continues to look for more opportunities to establish new or use existing ID/IQs. We carefully consider small business opportunities when establishing or using the ID/IQs. The advantages of establishing multiple award ID/IQs far outweigh the challenges. However, one challenge is once the contracts are awarded, new vendors tend to be unable to pursue NIH business for a period of time because so much of the ordering is limited to the existing contractors. Additionally, due to bid protests, NIH tends to award contracts to a large number of contractors rather than limiting the awardees to a smaller, more manageable pool. This tends to make the competition at the task order level less efficient. Small companies often feel the investment of time and energy expended when pursuing an ID/IQ is potentially wasted when the competition for individual task orders involves so many competitors and requires additional resources to receive the order. One last issue is the inability to award flexible orders when issuing task orders against multiple award ID/IQs. The firm nature of the orders often cause the NIH program to consider other arrangements such as a Blanket Purchase Agreement (BPA) against a GSA Schedule contract.

¹¹² <https://grants.nih.gov/grants/guide/pa-files/PA-16-217.html>.

¹¹³ <https://www.pbtc.org/>.

¹¹⁴ https://ctep.cancer.gov/MajorInitiatives/cancer_immunotherapy_trials_network.htm.

¹¹⁵ <http://www.nant.org/>.

¹¹⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-049.html>.

¹¹⁷ The foundation of this initiative began in 2017, with the release of two FOAs to establish the Pediatric Immunotherapy Discovery and Development Network (PI-DDN): <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-051.html>; <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-050.html>.

¹¹⁸ <https://ccr.cancer.gov/research/cancer-moonshot>.

¹¹⁹ <http://www.cancer.gov/researchandfunding/areas/childhood>.

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

FUNCTIONAL GENOMICS

Question. Fred Hutch researchers recently received NCI funds to continue work on an approach termed functional genomics, in which they focus directly on a patient's tumor cells. The approach can be applied toward different types of cancer, to pinpoint which drugs work best for an individual patient's tumor and identify drug resistance. With this new infusion of funding, researchers will have the opportunity to identify new drug targets in difficult to treat cancers and collaborate with various partners to help oncologists deliver individually tailored therapies to cancer patients. Can you tell me more about NCI's plans to support this type of highly targeted treatment?

Answer. The National Cancer Institute (NCI) is supporting a wide range of cancer genomic programs focused on understanding how cancer develops, the molecular changes that drive cancer, and the vast tumor heterogeneity within and across cancers. Precision oncology is rooted in a deep understanding of the genetic and functional changes that occur in cancer cells and the tumor microenvironment. NCI is committed to supporting research in genomics and other disciplines to increase our understanding of the complexity of cancer biology to advance precision oncology.

The NCI Center for Cancer Genomics (CCG) unifies NCI's activities in cancer genomics by aiming to synthesize research in different fields of cancer genomics. CCG's programs and collaborations generate cancer genomic and clinical data, and, importantly, make these data available for widespread use by the research community. Using a collaborative "team science" approach, CCG engages in three complementary sub-disciplines within cancer genomics: structural genomics, functional genomics, and computational genomics. Structural genomics identifies alterations in cancer that contribute to cancer growth, metastasis, and recurrence. Functional genomics studies the role of cancer genes, mutations, and pathways, and develops therapeutic strategies to target them. Computational genomics uses statistical and computational approaches to derive insight from big data on cancer. By testing hypotheses derived from structural genomics research, and by generating new ideas from experiments in cancer cells, functional genomics research reveals patterns in cancer biology that can be translated into novel therapies for precision cancer care.

To translate genomic insights to the clinic, the findings must be tested in models of cancer to understand the functional impact of insults to the genome. In addition to supporting investigator-initiated grants and other extramural research in this area, NCI provides resources to the extramural community to support their research on the molecular changes that drive cancer. One example is The Cancer Genome Atlas (TCGA),¹²⁰ which contains the genomes of more than 30 types of cancer and catalogues thousands of genetic alterations in cancer cells that could be targets for existing or new therapies. Another example is the Genomics Data Commons (GDC), a unified data system for sharing genomic and clinical data launched in 2016. The GDC centralizes, standardizes, and makes data from large-scale NCI programs more accessible and useful to scientists and clinicians. One measure of the importance of this resource is that non-profit and for-profit organizations are now offering their data sets for sharing through the GDC.

One program geared towards bridging the knowledge gap between data generated from large-scale genomic studies and the underlying etiology of cancer development, progression, and/or metastasis is the Cancer Target Discovery and Development (CTD)⁹⁶ Network. The CTD⁹⁶ Network is accelerating the use of molecular data to speed the translation of basic science findings to clinical trials. Through validation studies that rely on bioinformatics analysis of genomic data, high-throughput screening of small molecules, and research that involves cancer models or other tools, the CTD⁹⁶ Network supports research to capitalize on a growing volume of data to identify new cancer vulnerabilities and treatments.

The initial phase of CTD⁹⁶ Network generated 19 novel bioinformatic tools which enable the identification of therapeutic targets, gene and molecular networks, and driver mutations (genetic changes that drive the development of cancers), and chemical sensitivities. These tools are available to the scientific community and can be accessed through the CTD⁹⁶ analytical tools page.¹²¹ During the first phase, the Network has been highly successful and published over 60 manuscripts with pre-clinical and clinical relevance.⁹⁶ The results from some studies have provided sup-

¹²⁰ Collaboration with the National Human Genome Research Institute.

¹²¹ <https://ocg.cancer.gov/programs/ctd2/analytical-tools>.

porting evidence for the initiation of several clinical trials.¹²² Highlights of progress during this first phase include the discovering the mechanism of action of a compound that selectively inhibits the growth of breast cancer stem cells, and the discovery of novel, rare driver mutations in pancreatic cancer and confirmation of their importance through validation studies in model systems.

The second phase of the CTD⁹⁶ Network (multi-year awards funded in fiscal year 2017) is exploring cancer complexity in terms of various types of heterogeneity, that is differences in genetic characteristics within each patient (i.e., across tumor tissue, the tumor microenvironment, and normal tissue), as well as genetic differences within each tumor (i.e., different tumor cells may have different genomic characteristics and molecular drivers). Projects seek to understand the potential impacts of heterogeneity (i.e., acquired resistance to chemo and immunotherapies) and develop efficient strategies to overcome treatment resistance. Through active collaboration and the sharing of data and resources with the cancer research community, each of the twelve funded Centers within the CTD⁹⁶ Network will utilize functional and computational genomic approaches to contribute to the understanding of mechanisms of cancer and potentially accelerate the development of clinically useful markers, targets, and therapeutics for precision oncology.

Complimenting these efforts, NCI is supporting development of the Human Tumor Atlas Network (HTAN) as part of the Cancer Moonshot.SM The HTAN is planned to be a 5-year pilot consortium focused on generating comprehensive, multidimensional tumor atlases (detailed mapping of molecular and cellular characteristics) describing key transitions in the development of cancer that will inform future cancer research and, ultimately, clinical decisionmaking. The HTAN efforts build upon and extend the efforts of TCGA. The HTAN will draw upon the lessons learned from TCGA, address its limitations, and use evolving state-of-the-art information technology and other emerging technologies to achieve its goal. Additional efforts supported by the Cancer Moonshot,SM such as those focused on cancer immunology and immunotherapy, will increase our knowledge of genetic changes that occur in cancer cells and the tumor microenvironment to enable use of precision immunotherapy for both adult and pediatric cancer patients.

Currently ongoing Precision Oncology trials that utilize molecular characterization to inform treatment choice include the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) Trial and the Pediatric MATCH Trial. For these trials, rather than selecting therapies based on where a tumor originated in the body, the focus is on evaluating the effectiveness of treating cancer based on specific genetic changes. In 2017, the adult NCI-MATCH Trial achieved its enrollment goal, nearly 2 years ahead of schedule. The trial involves more than 6,000 patients from all 50 States. NCI also successfully opened enrollment for the Pediatric MATCH Trial in 2017. Other NCI precision medicine trials include the Lung Cancer Master Protocol (Lung-MAP) Trial, the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST), and Molecular Profiling-Based Assignment of Cancer Therapy (NCI-MPACT) Trial.

NCI's investment in cancer genomics programs such as the CTD⁹⁶ and the HTAN will inform future precision medicine trials and build upon the results of ongoing trials in this paradigm changing approach to precision oncology for cancer patients.

NCI-FUNDED RESEARCH

Question. Dr. Sharpless, cancer immunotherapy is one of the great success stories of NCI-funded research. After decades of basic research, patients today are receiving immunotherapy treatments for a growing number of cancers, including melanoma, lung cancer, lymphoma, leukemia, head-and-neck cancer, and more. Many of these patients previously had few other treatment options. Some who had even very advanced cancer are now doing extremely well. And, we are just getting started. What is being done to educate healthcare providers about the principles of immunotherapy and how to manage the toxicity? And what efforts is NCI taking to retrain laboratory scientists to advance the immunotherapy field?

Answer. Immunotherapy, a treatment that uses a patient's own immune system to help fight diseases including cancer, is a major focus of National Cancer Institute (NCI)-supported research that spans basic science to clinical applications. NCI-supported researchers publish their research results in peer-reviewed journals, and frequently present their research at professional conferences, including the annual meetings of the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO). For example, at the June 2018 meeting of ASCO, NCI-supported researchers participated in a two-day seminar entitled "Can-

¹²² <https://ocg.cancer.gov/programs/ctd2/publications>.

cer Immunotherapy Today: Maximizing Patient Outcomes,” co-hosted by ASCO and the Society for Immunotherapy of Cancer (SITC).¹²³ This session provided continuing education to clinical oncologists, nurses, pharmacists, and the entire medical team on effectively providing the most up-to-date and comprehensive immunotherapy options to their patients, and included guidance on patient selection and managing toxicities.

NCI supports training for immunotherapy investigators across the research spectrum, from basic to translational to clinical research. NCI’s Center for Cancer Research (CCR) supports an Immunotherapy Fellowship for physicians who have completed a medical oncology fellowship program and who seek specialized training in immunotherapy, including the design and facilitation of clinical trials.¹²⁴ Immunotherapy researchers are encouraged to apply for NCI-supported training awards.¹²⁵ Different awards are available to pre- and post-doctoral researchers, clinical fellows, established investigators, and non-tenured early-career stage faculty.

NCI’s intramural Center of Excellence in Immunotherapy (CEI) focuses on creating opportunities for immunologists in the intramural and extramural communities to exchange information and to facilitate collaborations. To that end, CEI sponsors an annual series of meetings on cancer-related immunology research, with the next meeting entitled “Frontiers in Basic Immunology”¹²⁶ planned for September 2018. Prior meetings included the 2017 “Cancer and Immunology and Immunotherapy: From Conception to Delivery,” meeting and the 2016 “Immunotherapy Biomarkers 2016: Overcoming the Barriers” meeting. Videos of the presentations and discussions are freely available online.¹²⁷

In addition to these resources, NCI plans to support new training and education efforts in fiscal year 2018 including supplemental training awards for cancer immunotherapy, and additional funding to support the development of a consortium. The consortium will engage external partners that will develop standardized educational content for oncology care providers and deliver the content nationwide.

NCI will continue to encourage the dissemination of research advances and the career development of the immunotherapy research community.

QUESTIONS SUBMITTED TO NORA VOLKOW, M.D.

QUESTION SUBMITTED BY SENATOR ROY BLUNT

CHRONIC PAIN

Question. Dr. Volkow, unfortunately, much of the opioid crisis we are experiencing today can be linked to opioid prescriptions to treat chronic pain. Your Institute has studied the effectiveness and risks associated with long-term opioid use for chronic pain, but what research is currently ongoing related to new and alternative options to treat chronic pain other than opioids?

Answer. In fiscal year 2017, NIH spent \$516 million on pain research ranging from cell and molecular mechanisms of acute and chronic pain to safe, effective therapy development, to large scale clinical trials. The portfolio includes many research projects that address the pressing need to develop new non-opioid, non-addictive, pain treatments. Research studies range from early-stage drug target discovery focusing on molecular pathways of pain signaling, including exploration of receptors and channels as potential non-addictive analgesic targets to testing in behavioral models. A number of targets identified through NIH basic science, such as nerve growth factor receptor and pain-related ion channels, are now being pursued in industry-sponsored clinical trials for non-addictive treatments. NIH supported early development of calcitonin receptor gene protein, a compound recently approved for migraine treatment.

A tissue-based tool for screening potential migraine drugs is under development and a library of small molecules is being leveraged to screen candidates for optimization as analgesics. Tissue engineering and regeneration to create tissue scaffolding and microenvironments to promote wound healing, joint cartilage, and intervertebral disc replacements is being applied to relieve pain. Neural stimulation technologies for chronic, intractable pain are being improved. For example, wearable

¹²³ <https://www.sitcancer.org/events/event-description?CalendarEventKey=796e7e32-bba9-4712-9491-daed98d7a3c8&Home=%2fevents%2fcalendar>.

¹²⁴ <https://www.cc.nih.gov/training/gme/programs/immunotherapy.html>.

¹²⁵ <https://www.cancer.gov/grants-training/training/funding>.

¹²⁶ <https://ncif-staging.ncifcrf.gov/Events/Conferences/Frontiers/>.

¹²⁷ <https://ncif-staging.ncifcrf.gov/Events/Conferences/Frontiers/PastConferences.aspx>.

ultrasound devices and implantable micro-stimulators are being tested on peripheral and central nervous system targets to relieve pain.

Evaluation and dissemination of complementary and integrative health approaches is a crucial component of quality pain management. NIH-supported studies include mechanism-based clinical studies on cognitive behavior therapy, exercise, yoga, acupuncture, massage, fitness, and mindfulness practices are an important component of the NIH Federal pain research portfolio.

QUESTION SUBMITTED BY SENATOR JOE MANCHIN, III

RESEARCH INTO ALTERNATIVE PAIN MANAGEMENT

Question. Dr. Volkow, communities across the country are seeing an alarming rise in substance abuse and addiction to prescription opioids. Opioids killed more than 42,000 Americans in 2016. That's 115 people every day. In West Virginia, we lost more than 909 people to a drug overdose in 2017.

So many of these people who become addicted started taking these drugs because their doctor prescribed them for pain even though—according to the CDC—there is little evidence that opioids improve chronic pain.

This is a public health crisis and we have to find a better way. I am proud to have worked with my colleagues to dedicate an additional \$500 million to NIH for research on opioid addiction, the development of opioid alternatives, pain management, and addiction treatment.

That is why I am so worried about the President's Budget Request to cut more than \$500 million from the National Institute on Drug Abuse.

Dr. Volkow, what research is being done to develop non-addictive alternative pain management options for patients—particularly those dealing with long-term, chronic pain who are currently being prescribed opioids despite the lack of evidence of their effectiveness?

What impact would the proposed budget cuts have on NIDA's ability to do continue to do this research?

Answer. Chronic pain is a complex neurological condition, driven by many biological, environmental, social, and developmental factors. To this end, NIH supports a range of activities to advance research on understanding and treating pain.

Chronic pain is a disorder of brain circuits, and the neurotechnologies emanating from the trans-NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative enable scientists to explore these circuits to advance diagnostics and therapeutics. Similarly, the Stimulating Peripheral Activity to Relieve Conditions (SPARC) program at the NIH Common Fund supports novel means to alter peripheral nerve pathways to relieve pelvic pain and has promise for application to other pain conditions.

Complementary and integrative health approaches address the biopsychosocial nature of chronic pain and its treatment. NIH supports numerous clinical studies on cognitive behavioral therapy (CBT), exercise, yoga, acupuncture, massage, fitness, and mindfulness practices. For example, trials showed that mindfulness-based stress reduction with CBT and yoga improved function and reduced low back pain.

The NIH Health Care Systems Research Collaboratory supports large-scale, pragmatic clinical trials focused on the management of patients with multiple chronic conditions, including pain. One study is evaluating multidisciplinary approaches to pain management in the primary care setting in patients who are currently on long-term opioids. This large-scale trial aims to develop integrated pain care approaches to reduce pain and opioid use in patients enrolled in a large healthcare system. The NIH, Department of Defense and Department of Veterans Affairs Pain Management Collaboratory's goal is to develop the capacity to implement cost-effective large-scale clinical research in military and veteran healthcare delivery organizations focusing on non-pharmacological approaches to pain management and other comorbid conditions.

To accelerate the development of novel non-addictive chronic pain medications and devices, NIH is establishing a Clinical Trial Network to optimize analgesic trial design, target appropriate patient populations for trials, and engage research expertise at existing clinical sites. A related initiative is to pursue, through the Network, development and validation of biomarkers of pharmacodynamic response and biomarkers for treatment response to optimize patient stratification based on phenotyping and thus allow smaller sample size and improve assay sensitivity for screening novel analgesics. These efforts provide a valuable set of clinical research resources which will allow researchers to identify effective pain medications more quickly.

The NIH Common Fund is currently in the planning stages of a broad scale clinical study to identify a set of objective biomarkers to predict which patients will transition to chronic pain after an acute pain event. This program, known as Acute to Chronic Pain Signatures Program, will collect longitudinal data from two large patient groups that have acute pain associated with a surgical procedure or an acute musculoskeletal trauma such as a bone fracture. Neuroimaging, genetic and molecular data, sensory testing, and psychosocial assessments from patients will be collected for months after the acute pain event and analyzed to explore transition or resilience characteristics to help predict which patients will recover and which patients will develop long-lasting pain. Identifying such markers will help to predict which people might be at risk for developing chronic pain, reducing reliance on opioids thereby, guide precision medicine approaches to prevent chronic pain, and by doing so, reducing our reliance on opioids.

The current state of the science, emerging technologies, and mobilization of the research community holds great promise for advances in evidence-based, quality pain care.

SUBCOMMITTEE RECESS

Senator BLUNT. The subcommittee stands in recess.

[Whereupon, at 11:38 a.m., Thursday, May 17, the subcommittee was recessed, to reconvene subject to the call of the Chair.]

MATERIAL SUBMITTED SUBSEQUENT TO THE HEARING

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

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

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

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

ACCELERATING CLINICAL TRANSLATION

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

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

Providing the resources to train, cultivate, and sustain future leaders of the biomedical research workforce is another key CTSA Program emphasis. The program supports a coordinated, national effort to help ensure a pipeline of trained translational investigators who can move basic research findings into applications for improving health outcomes as novel therapies, diagnostics, and preventives. Program grantees have developed clinical and translational sciences training resources, including educational core competencies, best practices for training mentors, and curriculum materials. These tools are freely available, and many institutions nationwide are using them.

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

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

FINDING NEW THERAPIES FOR CLINICAL STUDY

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

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

The NCATS Cures Acceleration Network (CAN) supports high-risk, innovative programs to advance the development of high-need cures and reduce significant barriers between research discovery and clinical trials. Through the CAN-funded Tissue Chip for Drug Screening program, NCATS is working on new methods for predicting both safety and efficacy of experimental drugs using engineered "chips" that contain human cells and model human organs. Current methods such as animal and cell models are not always reliably predictive and can result in wasted time and effort. In addition to developing these chips for testing potential drugs, NCATS soon will send tissue chips to the International Space Station (ISS) for research on the effect of microgravity on these model organs. Microgravity can accelerate aging and have other effects relevant to diseases on Earth, making the ISS a unique and significant research environment.

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

ADAPTABILITY TO TACKLE EMERGING PUBLIC HEALTH NEEDS

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

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

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

CONCLUSION

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

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 2019 budget request for the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health (NIH).

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

PREVENTING HEARING LOSS CAUSED BY COMMON CANCER DRUG

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

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

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

TREATING HEREDITARY DEAFNESS WITH GENE EDITING

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

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

The researchers developed a novel approach to deliver the gene-editing complex into the inner ears of newborn mice. They packaged the gene-editing complexes in lipids (fats) that form structures called liposomes. The liposome-packaged complexes move readily through cell membranes into cells. Eight weeks later, substantially more hair cells survived in ears of treated compared to untreated mice. The treat-

ment also significantly reduced progressive hearing loss. This novel strategy may help scientists develop new therapies for hearing loss caused by inherited genetic mutations.

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

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

The identity of this “sour detector” protein has been elusive. Now, NIDCD-supported scientists have located a protein called OTOP1 and determined that it forms a channel that allows protons to enter taste cells on the tongue. They have also confirmed that human OTOP1 forms a channel with properties similar to those of the mouse OTOP1 protein. When OTOP1 gene was altered in mice, the scientists observed that taste cells had significantly fewer protons going into them. This evidence, together with other supporting studies on OTOP1, suggests that OTOP1 is the long-sought after sour taste receptor. The next step to test this theory will be to record whether mice that lack OTOP1 respond to sour tastes. Studies like this one, that increase our understanding about how we taste, may help scientists learn to restore a sense of taste to those who have lost it due to disease or injury.

This study may help us understand far more than just how we detect taste. OTOP1 is also required for the vestibular (balance) system in the inner ear to detect gravity, so it is important for helping us keep our balance. OTOP1 is also expressed in many other body tissues, including fat, heart, uterus, breast, and the nervous system. Since we know that OTOP1 functions as a proton-sensitive channel, what we learn from this taste study may help us understand cell signaling in these other tissues, too. When protons enter cells, they change the acid/base (pH) concentration. So, a better understanding of OTOP1 could also help us understand other body processes that involve changes in pH, such as pain sensation, fat metabolism, and pH changes seen in cancer cells.

PERSONALIZED VOICES FOR PEOPLE WITH SEVERELY IMPAIRED SPEECH

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

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

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

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

ACHIEVING LIFELONG HEALTH

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

Child Health.—The epidemic of opioid use disorder and its consequences is among the most serious public health threats in this country today. Among those exposed to opioid use are the thousands of infants born to women with the disorder. Every 15 minutes, a baby is born with Neonatal Opioid Withdrawal Syndrome (NOWS) in the United States; to date, NOWS has cost about \$2 billion in additional costs for Medicaid-financed deliveries.¹ Symptoms of NOWS, also known as Neonatal Abstinence Syndrome (NAS), often do not begin until after infants have been discharged from the hospital. Their needs are placing huge stresses on the healthcare and foster care systems nationwide. To address this problem, NIH launched a new study called the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) to evaluate treatment options and improve clinical care of affected infants. The study is a collaboration between NICHD's Neonatal Research Network and the new IDEa States Pediatric Clinical Trials Network (within the Office of the NIH Director's Environmental Influences on Child Health Outcomes program), with sites located in rural and medically underserved communities. This joint research effort will use the reach of both networks to assess the prevalence of NOWS, understand current approaches to managing these cases, and develop protocols for conducting large scale studies to inform clinical care, so that these babies may get a better start in life.

One of NICHD's longest standing research priorities is to improve the lives and health of people with intellectual and developmental disabilities, such as Down syndrome. NICHD leads the public-private Down Syndrome Consortium, which includes 11 NIH Institutes and Centers, 13 national and international organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members. Consortium members provided valuable input to DS Directions: The NIH Down Syndrome Research Plan. Among the plan's major objectives is the call for research on the co-existing conditions commonly experienced by people with Down syndrome. For example, studies show that virtually all middle-aged adults with Down syndrome exhibit the neuropathological hallmarks of Alzheimer's disease, 50 percent of whom will develop this type of change to the brain by age 40. Funded jointly by NICHD and the National Institute on Aging, a new project, the Alzheimer's Biomarker Consortium—Down Syndrome (ABC-DS), seeks to identify biomarkers and use brain imaging to help us understand the progression of the disease. In addition, the research teams will make their data and samples freely available to qualified researchers worldwide, with the goal of accelerating the testing of potential interventions, which in turn may have widespread implications for Alzheimer's and other conditions. In fiscal year 2018, NICHD will lead a major new initiative to explore the risk and resilience of people with Down syndrome to common, co-existing conditions such as autism, cancer, and cardiovascular disease.

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

¹ Winkelman, T.N., Villapiano, N., Kozhimannil, K.B., Davis, M.M., Patrick, S.W., Incidence & Costs of Neonatal Abstinence Syndrome among Infants with Medicaid: 2004–2014, *Pediatrics* published online: March 23, 2018 (doi: 10.1542/peds.2017–3520).

children who are engaged during shared reading experience a boost in the area of the brain that is involved in language development, comprehension, memory, and problem solving; understanding how reading shapes a child's brain can help educators and parents develop and use effective early learning strategies.

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

NICHD is supporting two major projects to gather unprecedented amounts of information about pregnancy. Its ongoing Human Placenta Project, designed to provide insights into placental health noninvasively and in real time, continues to yield new data to improve maternal health and pregnancy outcomes. Another effort launched this year, PregSource® is a longitudinal, crowd-sourced, citizen science registry that will expand our knowledge about women's typical experiences during pregnancy and after birth, the effects of pregnancy on women's lives, and special health challenges some women face. In addition, many pregnant or breastfeeding women must either take prescription medications to ensure their own health or are urged to take medications to benefit the baby's health outcomes. As part of the 21st Century Cures Act legislation, NICHD was asked to lead the newly mandated Federal Task Force on Research Specific to Pregnant Women and Lactating Women. Although pregnant women in the United States take between three and five prescription medications, usually for serious health conditions, very few of these therapies have been tested during pregnancy. Almost nothing is known about the transfer of medications into breast milk, nor the risks and benefits of breastfeeding while on medication. The Task Force's report and recommendations are due to the Secretary of Health and Human Services and Congress by September 2018, which will shed light on this understudied issue.

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

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

CONCLUSION

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

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 2019 budget request for the National Institute of Environmental Health Sciences of the National Institutes of Health (NIH).

TEAM SCIENCE FOR HEALTH SOLUTIONS

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

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

CENTERS, CONSORTIA, AND COLLABORATIONS

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

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

Consortia are another way that NIEHS supports team science that extends beyond a single institution to create a network of linked expertise to focus on a complex environmental health problem or set of related issues. NIEHS led the Gulf Long-term Followup (GuLF) Study and the 5-year, \$25.2-million Deepwater Horizon Research Consortia, both of which partnered researchers with communities to investigate health effects stemming from the oil spill, including the long-term mental health impacts of the spill on coastal residents, especially women and children; the resilience of individuals and communities; and whether seafood in the Gulf was safe

for human consumption. These research partnerships continue to yield new insights: a 2017 study linked a range of health problems in workers who were exposed to dispersants used to clean up the oil spill.

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

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

Perhaps the most prominent environmental hazard demanding a team science approach from across a broad spectrum of disciplines is lead exposure. NIEHS-supported science established the knowledge base for lead's major health impacts. But although we understand the primary outcomes of lead poisoning, particularly neurodevelopmental damage in children, the need continues for research to make clear exactly how lead works in the body to cause damage so that successful interventions can be developed. An NIEHS-funded study using lead in baby teeth as a marker of exposure found associations between lead levels just before and after birth with the risk for and severity of autism in later childhood. Another study of children whose mothers took multivitamins during pregnancy suggested they were 30 percent less likely to develop autism. The concerns are not just for children however; a recent study estimated that low-level lead exposure ($<5\mu\text{g/dL}$ blood) is responsible for more than 400,000 deaths each year in the United States, some 250,000 of which from cardiovascular disease in adults. Combined with the estimated half million children still exposed beyond the CDC reference level, the health, economic, and societal consequences of lead exposure remain great. NIEHS and our grantees are continuing to respond to this threat through research, training for workers involved in lead cleanup and remediation, and engaging with our Federal partners on the President's Task Force on Environmental Health Risks and Safety Risks to Children to develop a Federal Lead Strategy.

CONNECTING THE DATA POINTS

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

and prioritization of data science and integration goals across our developing Strategic Plan.

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

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

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

ACCELERATING BIOMEDICAL DISCOVERY & DATA-POWERED HEALTH

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

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

RESEARCH IN BIOMEDICAL INFORMATICS AND DATA SCIENCE

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

Research in data science produces novel analytical approaches and visualization tools that help scientists accelerate discovery from data and translate these findings to clinical solutions. It also aims to solve problems consumers face in accessing, storing, using, and understanding their own health data and to produce tools that make precision medicine discoveries available and more understandable to patients. Biomedical informatics research is yielding advanced analytical methods and tools for use against large scale data generated from clinical care, leading to fuller understanding of the effects of medications and procedures as well as individual factors important in the prevention and treatment of disease processes.

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

NLM's biomedical informatics research also addresses issues in computational biology. Research creates new ways to represent and link together genomic and bio-

logical data and biomedical literature and produces analytic software tools for gaining insights in areas such as genetic mutational patterns and factors in disease, molecular binding, and protein structure and function.

BIOMEDICAL INFORMATION SYSTEMS FOR RESEARCH AND HEALTH

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

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

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

ENGAGING THE PUBLIC WITH HEALTH INFORMATION

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

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

CONCLUSION

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

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 2019 budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

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

RESEARCH ON INFECTIOUS DISEASES

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

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

Zika. NIAID research has led to the rapid development of diagnostics, candidate vaccines, and therapeutics to address the public health threat of Zika virus disease, especially Zika virus-related congenital abnormalities. NIAID scientists developed a DNA-based Zika vaccine that is now being tested in a large-scale clinical trial in Zika-endemic regions. NIAID is developing other candidate Zika vaccines, including a live, attenuated vaccine that targets both Zika virus and the related dengue virus. In addition, NIAID is partnering with other NIH Institutes and the Fiocruz Institute in Brazil to support the Zika in Infants and Pregnancy cohort study, which is assessing the risks of Zika infection in expectant mothers and tracking infant outcomes for at least 1 year.

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

HIV/AIDS. NIAID research has led to powerful HIV treatment and prevention tools that improve the lives of individuals living with HIV and that have the potential to eventually end the HIV/AIDS pandemic. NIAID is supporting new HIV vaccine studies, including the Imbokodo trial in sub-Saharan Africa that is evaluating

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

Tuberculosis. NIAID supports research to address tuberculosis (TB) including the challenges of TB/HIV co-infection and increasing drug resistance. NIAID also leads the research component of the National Action Plan for Combating Multidrug-Resistant TB. NIAID scientists and collaborators have developed a new diagnostic tool that detects resistance to key antibiotics used to treat TB and may facilitate a point-of-care diagnostic approach to guide TB therapy. In addition, an NIAID clinical trial of HIV-infected individuals demonstrated that a 1 month course of preventive TB medication was as safe and effective as a nine-month regimen. Patients were more likely to complete the short regimen, suggesting it may be a preferred TB prevention strategy.

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

RESEARCH ON IMMUNOLOGY AND IMMUNE-MEDIATED DISORDERS

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

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

Stem Cell Transplants for Treatment of Autoimmune Diseases. Two recent NIAID-supported clinical trials found that intensive immunosuppression followed by transplantation of a patient’s own stem cells was an effective treatment for progressive and life-threatening autoimmune diseases. The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial showed that stem cell transplantation improves survival and quality of life for people with severe scleroderma when compared with routine immunosuppression. The HALT-MS trial demonstrated sustained remission in most people with relapsing-remitting multiple sclerosis for 5 years following transplantation.

CONCLUSION

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

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 2019 budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

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

INVESTING IN BASIC RESEARCH TODAY FOR TOMORROW'S CURES

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

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

THE POWER OF DATA TO PERSONALIZE MEDICINE

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

Data from TOPMed will be included in a pilot of the new NIH Data Commons, a public-private partnership to bring research findings into a cloud-computing environment to enhance data sharing. This effort will give researchers access to data from hundreds of studies, creating new opportunities for collaborative research, innovation, and discovery.

REDUCING HEALTH DISPARITIES

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

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

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

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

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

to disease awareness, prevention, and treatment, reflected in a high burden of CVD risk factors such as high blood pressure, smoking, low physical activity, and high-calorie diets.

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

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

SICKLE CELL DISEASE: FROM BETTER TREATMENTS TO A CURE

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

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

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

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

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

CONCLUSION

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

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

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

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 2019 budget request for the Fogarty International Center (FIC) of the National Institutes of Health (NIH).

INTRODUCTION

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

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

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

STRENGTHEN AND SUSTAIN THE BIOMEDICAL WORKFORCE

Global Health Security

Emerging epidemics such as Ebola demand a critical mass of in-country scientists with relevant research expertise and skills. In 2016, Fogarty initiated the Emerging Epidemic Virus Research Training for West African Countries with Widespread Transmission of Ebola program. These grants fund collaborations between U.S. and African research institutions in Guinea, Liberia, and/or Sierra Leone to plan capacity building programs for Fogarty's Global Infectious Disease Research Training Program, with a focus on emerging viral epidemics. This support enables scientists on the front lines in these countries, which were ground zero for Ebola, to design training programs that increase expertise in Ebola, Lassa fever, and other emerging viral diseases. For example, Yale University, in partnership with the University of Liberia, will develop a training program focusing on predictive transmission modeling and epidemiological research. Fogarty has also awarded a grant to Tulane University, the Vanderbilt Institute for Global Health, and the University of Sierra Leone. Together, these institutions will advance research focused on efficacy studies of novel and existing therapeutics for endemic viral hemorrhagic fevers like Lassa fever, while simultaneously building capacity on how to conduct higher-level clinical trial research during an epidemic like Ebola.

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

Combatting Common Disease Threats

Fogarty also supports training of scientists in LMICs, many of whom have become leaders in academic institutions and ministries of health in their home countries and serve as critical partners for U.S. scientists. Notably, many health challenges facing Americans are most effectively addressed through research conducted in a global context, where diseases are often highly prevalent or where the study of

unique genetic predispositions can inform how we detect and prevent certain diseases that affect U.S. citizens.

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

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

RESEARCH

Brain Disorders. Fogarty's Global Brain and Nervous Systems Disorders Research across the Lifespan Program supports cutting-edge research in LMICs on nervous system development, function, and impairment throughout life. The program allows U.S. investigators to gain experience working in LMICs, expanding the research workforce in these settings by developing long-lasting international partnerships. This research network spans over 45 countries and has contributed to the creation of new interventions, new tools for clinical assessment, and new laboratory methods.

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

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

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

CONCLUSION

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

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

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

FUNDING IMPACTFUL SCIENCE TO ALLEVIATE BURDEN

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

EARLY IDENTIFICATION AND INTERVENTION

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

Suicide is a potential consequence of mental illnesses and one of the leading causes of mortality in the United States. Suicide rates have increased since 1999, and nearly 45,000 Americans died from suicide in 2016. Recent studies show that most individuals who die by suicide have had recent contact with a healthcare provider, and that early identification of those at risk for suicide is key to prevention. To address this major public health concern, NIMH partners with the National Action Alliance for Suicide Prevention and supports its Zero Suicide initiative to support healthcare systems reduce suicide events. Another example of NIMH-funded work in this area is the ED-SAFE project, which demonstrated that universal screening for suicide risk among adults in emergency departments (EDs) doubled the rate of detection, and ED-initiated interventions for high-risk adults decreased suicide attempts by as much as 30 percent.

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

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

for ASD for use in infants (0–12 months of age) which could lead to novel transformative treatments that improve outcomes.

DEVELOPING EFFECTIVE AND TRANSFORMATIVE TREATMENTS OF TOMORROW

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

It is ever important that we continue to support research focused on developing tools that can be used to study and treat mental illnesses. For example, NIMH co-leads the cutting-edge NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Maps of whole brains in action, the ability to identify thousands of brain cells at a time, and innovative brain scanners are just a few of the advances funded by this groundbreaking effort. In the past 3 years, research under the Initiative has advanced so rapidly that now many of the previously funded individual projects will receive expanded support to achieve the ambitious goals of the BRAIN Initiative.

Specifically, NIH recently announced funding for 110 new awards for the BRAIN Initiative. The new round of awards includes the BRAIN Initiative Cell Census Network (BICCN), aimed at providing researchers with comprehensive references of diverse brain cell types to generate the knowledge necessary for understanding brain disorders, including mental illnesses. Additionally, new BRAIN Initiative research awards aim to address neuroethical issues associated with human brain research. Through the innovative studies supported by the BRAIN Initiative, researchers will be able to produce a revolutionary, dynamic picture of the brain that will lend to new ways to treat, cure, and even prevent mental illness.

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

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

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 2019 Budget request for the National Institute of Nursing Research (NINR) of the National Institutes of Health (NIH).

INTRODUCTION

The mission of NINR is to promote and improve the health of individuals, families, and communities. In pursuit of this mission, NINR has set forth a bold, innovative scientific agenda in our strategic plan, “Advancing Science, Improving Lives.” The plan, which incorporates long-standing focus areas of nursing science and 21st century solutions for improving the Nation’s health, encompasses four focus areas, including symptom science, wellness, self-management, and end-of-life and palliative care; along with continued development of a 21st-century nurse scientist workforce,

and finding ways in which technology and innovation can contribute across all these areas. I appreciate this opportunity to share some examples of NINR's research.

SYMPTOM SCIENCE: PROMOTING PERSONALIZED HEALTH STRATEGIES

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

WELLNESS: PROMOTING HEALTH AND PREVENTING ILLNESS

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

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

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

SUPPORTING A 21ST CENTURY NURSING SCIENCE WORKFORCE

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

CONCLUSION

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

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

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

THE FOREFRONT OF GENOMICS

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

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

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

As noted earlier, the uptake of genomic medicine approaches will increase rapidly in the coming years, and NHGRI is committed to laying the groundwork for these changes. An example effort that will be underway in fiscal year 2019, if funding allows, is the Clinical Sequencing Evidence-Generating Research Program (CSER), which aims to generate and analyze evidence for the use of genome sequencing in clinical care and to address barriers to genomic medicine implementation. This program has a targeted focus on recruiting ancestrally diverse and underserved populations, recognizing that the full benefit of genomic medicine will not be realized unless all of the diverse populations in the United States benefit equitably from genomic advances.

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

RESEARCH

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

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

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

Another treasure trove of data for the biomedical research community was generated by the NHGRI-led Common Fund project GTEx (genotype-tissue expression), which began in 2008 and aimed to establish a database and accompanying tissue bank to allow scientists to study the relationship between genomic variation and gene expression. In October 2017, *Nature* published a collection of papers highlighting discoveries from the program. The analyses include data for thousands of tissue samples and demonstrated how gene regulation differs across individuals and tissue types.

NHGRI has also been building its portfolio in genomic medicine, piloting projects that seek to explore how to integrate genome sequencing within clinical care and begin to build an evidence base demonstrating its effectiveness. One example is the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, which began in 2013 to study the opportunities and challenges in the use of genome sequencing for the care of newborns. NSIGHT has shown ways in which newborn sequencing can be critical for saving lives by increasing the speed of diagnosis. For example, one of our NSIGHT grantees, whose work was recently featured in *Time* magazine, is using genome sequencing to provide diagnoses and suggest treatment changes for critically ill infants in the neonatal intensive care unit in a timeframe that can make life-altering differences.⁷ Notably, this group recently set a Guinness World Record for the fastest genomic diagnosis—19.5 hours.

CONCLUSION

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

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

⁷ Park, A. (2017) Genetic Testing is Providing New Hope for Babies Born with Mysterious Ailments. *Time*. <http://time.com/4951200/genetic-testing-providing-hope-babies-ailments/>.

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

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

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

ON THE SPOT FOOD ALLERGY TESTING

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

CUFF-LESS BLOOD PRESSURING MONITORING

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

CLEARING OUT BLOOD CLOTS

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

NANOVACCINES WEAPONIZED TO BATTLE TUMORS

A new vaccine designed to stimulate a multi-pronged immune response can stimulate the immune system to specifically attack a tumor, while simultaneously inhibiting the suppression of the immune system, which often occurs in people with cancer. The researchers also developed a way to shrink the vaccine molecule so that it can more easily reach the parts of the immune system to activate it. Using colon

cancer that had spread to the lungs as a test case for this approach, the nanovaccine successfully blocked lung tumor growth in a mouse model. Further testing revealed that mice receiving the nanovaccine had a significant increase in a type of immune cell that can target cancerous cells. Another potential benefit of this approach is that it mounts an anti-tumor immune response that circulates through the system, and therefore is particularly valuable for finding and inhibiting metastatic tumors growing throughout the body.

SOLVING A COMMON HEART DISEASE WITH ENGINEERING

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

ADVANCES FROM NIBIB LABORATORIES

While the majority of NIBIB's budget supports research projects throughout the U.S., NIBIB also supports a small, but robust program within its Intramural Research Program (IRP). These investigators are working to create optical imaging technologies that provide unprecedented high resolution and speed to study living cells in real time. Others create "theranostic" imaging probes—based on nanomaterials—that combine therapeutic and diagnostic capabilities to improve early diagnosis, monitor therapeutic responses, and guide drug discovery and development.

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

CONCLUSION

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

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

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

AGING: A UNIVERSAL RISK FACTOR

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

At the NIH, the NIA leads this effort. We support genetic, biological, clinical, behavioral, and social research related to the aging process, healthy aging, and diseases and conditions that increase with age. We also support training of the next

generation of researchers in geriatrics and related fields. In addition, we are the lead Federal agency supporting research on Alzheimer's disease and related forms of dementia (AD/ADRD).

RESEARCH ON ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

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

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

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

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

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

ADVANCING AGING RESEARCH

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

NIA's longtime flagship studies in aging remain vibrant with opportunities to apply new technologies and thinking to their treasure troves of data. The Baltimore

Longitudinal Study on Aging, 60 years old in 2018, continues to break new ground in identifying the longitudinal physical and cognitive changes that define aging; elucidating the factors that affect the rate of age-related change; and understanding the relationship between advancing age and chronic disease. BLSA investigators are particularly interested in “exceptional agers”—those rare individuals who live well into their eighties with few health problems. This year the Health and Retirement Study (HRS) will complete 25 years of data collection and will mark the occasion with several enhancements, including deployment of an improved approach to assessing cognitive impairment and dementia and expanded collection of objective health measures, including blood-based assays capturing the aging of the immune system and related molecular and cellular age-related changes. This project and others are designed to reveal the biological pathways through which differences among social and demographic groups can affect health.

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

EMPOWERING THE NEXT GENERATION OF SCIENTISTS

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

Thank you. I welcome your questions.

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 2019 budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH).

NIAMS RESEARCH IMPACTS EVERYONE

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

NIAMS is enhancing health, lengthening life, and reducing illness and disability by supporting basic and translational research and clinical trials that will inform

medical practice; training the next generation of bone, joint, muscle, and skin scientists; and disseminating health information and the findings from the studies it supports to all Americans. For the remainder of my statement, I will describe a few of the many recent research activities that are benefiting people today and enabling future advances.

RESEARCH ADVANCES FUNDED BY NIAMS

My first two examples focus on the risks and benefits of steroids, which an estimated 1 percent of the entire U.S. population takes as chronic therapy. A team of researchers studying the effects of repeated steroid injections for knee pain found that people who received shots every twelve weeks for 2 years showed worsening joint damage and no long-term reduction in pain compared with those who received saline injections. While this study did not evaluate the benefits of steroid injections into the knee for short-term pain relief, it does not support their long-term use for treatment of symptomatic knee osteoarthritis. Another group of investigators looked at the mechanisms by which steroids preserve muscle function for boys who have Duchenne muscular dystrophy. Using cells and a mouse model, the team determined that a weekly dosing regimen increases the activity of two genes involved in muscle cell repair, while daily dosing activates pathways that cause muscle to shrink and weaken. Their discovery explains the seemingly contradictory results of previous studies into the drugs' effects. If these observations from cell cultures and mice also occur in patients, this study could directly inform how steroids are prescribed to maximize their therapeutic benefits while minimizing their negative effects.

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

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

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

NIAMS-funded research is also having an impact beyond arthritis and musculoskeletal and skin diseases. For example, psoriasis has been linked to an increased

risk of developing type 2 diabetes. A new finding that the risk of diabetes is highest for those with the most severe psoriasis sheds light on the causes of both diseases and provides compelling evidence that certain patients should receive targeted diabetes prevention strategies. Other investigators are showing that while early antiretroviral therapy saves HIV patients' lives, it also damages their bones, emphasizing the importance of developing bone-preserving strategies for this population. Weight loss due to bariatric surgery, another life-saving intervention, also is associated with bone loss, and researchers are beginning to understand the role that glucose metabolism plays in bone health. This discovery could lead to targeted prevention and treatment strategies for osteoporosis, the skeletal complications of bariatric surgery, and diabetic bone fragility. Still other research is explaining why muscle breaks down in cancer patients (a process known as cachexia). A number of molecular pathways and targets underlying the muscle wasting process have been discovered recently, and investigators are beginning to identify existing drugs or new targets to stop this from occurring.

LOOKING TO A PROMISING FUTURE

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

In fiscal year 2019, NIAMS plans to continue support for its Research Innovations for Scientific Knowledge (RISK) funding opportunities, which allow investigators from around the country to submit cutting edge, unconventional, innovative research proposals for up to 3 years of funding. To help bolster the next generation of researchers, the Institute also continues to encourage early established investigators who have successfully renewed their first NIAMS research project grant to apply for a supplemental funding program to aid the transition of their individual research project into a broader, more robust and resilient research program.

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

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

BURDEN OF ALCOHOL MISUSE IN THE UNITED STATES

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

ADVANCING TRANSLATIONAL AND CLINICAL RESEARCH

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

the way for the development of novel strategies to address medical conditions associated with alcohol misuse.

Alcohol Treatment NavigatorSM

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

Addiction Medicine in Routine Healthcare

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

Alcohol-Associated Liver Diseases

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

Fetal Alcohol Spectrum Disorders

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

EMERGING PUBLIC HEALTH ISSUES

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

Increases in Alcohol-Related Emergency Department Visits

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

Extreme Binge Drinking

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

Alcohol Misuse Among Women

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

Alcohol Misuse Among Older Adults

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

CONCLUSION

Advances in alcohol research have expanded our knowledge of the effects of alcohol on health and resulted in numerous evidence-based preventive and treatment interventions. Still, more work needs to be done to reduce the burden of alcohol misuse in our Nation. With its fiscal year 2019 budget, NIAAA will continue to invest in basic, clinical, and translational research to address existing and emerging public health concerns and cultivate the biomedical research workforce to harness the contributions and perspectives of the broadest range of investigators.

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

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

THE CHALLENGE OF NEUROLOGICAL DISORDERS

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

PROGRESS AGAINST NEUROLOGICAL DISORDERS

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

- Stroke*.—Two decades ago, NINDS-supported research showed that tPA therapy can restore blood flow to the brain following a stroke. For the first time, stroke became a treatable emergency, and the care system organized to take advantage. Building on NINDS funded research, clinical trials in 2015 showed that timely intervention with intravascular devices can directly clear a blocked brain artery in severe strokes when tPA does not restore blood flow, with striking clinical benefit. In 2018 the NINDS DEFUSE 3 clinical trial reported that a brain imaging method can identify people who may respond well beyond the current restricted time window for this intervention, now up to 16 hours, so many more people with strokes may benefit.⁸ These recent results again transform emergency stroke treatment, and stroke care systems are now making these catheter-based treatments available in both urban and rural communities.
- TBI*.—The 2018 FDA marketing authorization of the first blood test to help in the diagnosis of concussion exemplifies the extensive NIH and DoD cooperation on TBI. NINDS funded the foundational basic science and clinical studies to the successful research team, and DoD supported the subsequent development and testing. The test could reduce the cost and radiation exposure from thousands of unnecessary CT scans.
- New Drugs*.—Pioneering NIH-supported basic and translational research, and subsequent private sector development, led to FDA approval of the first disease-modifying drugs for two rare pediatric diseases, spinal muscular atrophy (SMA) and Batten disease. The FDA also approved the first drugs for primary progressive multiple sclerosis, for movement problems associated with Huntington's disease, and a drug for amyotrophic lateral sclerosis (ALS). And researchers reported promising results for migraine, adrenoleukodystrophy, Niemann-Pick disease, and several other disorders.
- Dementia*.—A long-term NIH study with more than 15,000 people found that middle aged Americans who have vascular risk factors, including diabetes, high blood pressure and smoking, are more likely to suffer from dementia later in life.⁹ The findings add to a growing body of evidence linking cardiovascular health to brain health. The hope is that managing vascular risk factors in middle age may slow or prevent the development of dementia, and there are hints that may be happening.¹⁰

DRIVING FUTURE PROGRESS

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

⁸N Engl J Med. 378:708–718 2018.

⁹JAMA Neurology 74:1246–54 2017.

¹⁰New England Journal of Medicine 374:523–32, 2016.

- The Opioid Crisis*.—Through a series of workshops and discussions in 2017, Federal agencies, the scientific community, and industry forged a partnership to accelerate the development of safe and effective, non-addictive treatments for pain. NINDS leads two key priorities of the plan— development of biomarkers (objective indicators) of pain and of a clinical trials network to use biomarkers for the development of non-addictive pain treatments. Together with the NIH Pain Consortium and the NIH Director's Common Fund, NINDS is also targeting the key question of why acute pain leads to chronic pain for some people, well after the original cause of pain has been resolved.
 - ADRDs*.—Through the National Alzheimer's Project Act (NAPA), Congress recognized the impact of not just Alzheimer's, but also Alzheimer's disease-related dementias (ADRDs). Frontotemporal dementia (FTD) is the most common dementia in people younger than 60, and Lewy body and Parkinson's dementias also have a major impact. The most common ADRD, Vascular Cognitive Impairment and Dementia (VCID), like stroke, affects brain blood vessels. VCID is so intertwined with Alzheimer's disease that most elderly people with dementia have a combination of the two. NINDS leads several new and ongoing initiatives to understand and develop treatments for the ADRDs, working closely with the National Institute of Aging (NIA), which provides funding to a suite of these NINDS-led programs. NINDS also leads the ADRD summits that occur every third year, as mandated by NAPA.
 - AMP PD*.—NINDS, Celgene, Verily, Pfizer, GlaxoSmithKline, Sanofi, the Michael J. Fox Foundation (MJFF), and the Foundation for NIH are launching the Accelerating Medicines Partnership for Parkinson's Disease (AMP-PD). This new addition to the NIH AMP program will identify and validate biomarkers and new therapeutic targets for Parkinson's disease, leveraging a treasure trove of data and resources supported over the past several years by NINDS, MJFF, and others.
 - Pediatric Concussion*.—An NINDS initiative will develop biological measures of persistent symptoms following pediatric concussion, which addresses the highest research priority identified by a 2016 NIH scientific workshop on pediatric concussion.
 - Biomarkers*.—The lack of reliable biomarkers for most neurological disorders heightens the challenges of developing treatments and dissuades private sector investment. An NINDS initiative will support the advanced development and validation necessary to bring potential biomarkers to clinical practice, complementing the extensive early phase biomarkers discovery research that is already underway.
 - BRAIN Initiative*.—NINDS is an enthusiastic leader of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. The Initiative is developing and applying new technologies to understand how circuits of interconnected nerve cells in the brain enable us to perceive, act, think, and learn, and what goes wrong in brain disorders. Remarkable new tools now enable researchers to identify all of the individual brain cell types, monitor activity of thousands of cells in a circuit at once in real time, precisely manipulate cells' activity, and non-invasively monitor and stimulate the human brain with increasing precision. As the Initiative continues, engaging these new opportunities to enhance research on pain and addiction is a high priority.
- Finally, NINDS continues its longstanding emphasis on investigator-initiated basic research, which is yielding remarkable advances on many fronts in addition to circuits. Among the many findings this year, for example, research discovered unexpected links between bacteria and brain blood vessels, new roles of non-nerve cells in the brain, insights about how genes orchestrate brain development, the role of undetected seizure-like activity in Alzheimer's disease, how the gut conveys information to the nervous system, mechanisms of memory, and novel ways that nerve cells respond to stress. Which findings from basic research will launch the next advances against disease is not yet apparent. However, NIH basic research will surely continue to be the wellspring of progress for both the public and private sector.

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

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

The NIGMS focuses on promoting and supporting fundamental or "basic" biomedical research that increases scientific knowledge about how living systems work,

from individual molecules to cells, organs, whole organisms, and populations. The Institute's priority is to support investigator-initiated research, based on the principle that the best scientific ideas, directions, and approaches stem from scientists themselves. Thus, NIGMS aims to enable creative, innovative, and ambitious research conducted by individuals and teams of investigators to promote scientific discovery and medical advancement.

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

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

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

In order to enhance the efficiency and productivity of fundamental biomedical research, the NIGMS has developed a new mechanism to fund scientists. The Maximizing Investigators' Research Award (MIRA) seeks to transform how fundamental biomedical research is supported by providing individual investigators with a heightened level of both scientific stability and flexibility.¹¹ These awards allow investigators to follow new research directions and insights in real-time, while simultaneously providing an extra year of support as part of a more coordinated scientific program (versus single project) focus. In addition, the peer review process for MIRA applicants reviews early stage investigators (ESIs) independently from established investigators (EIs), thus allowing each group of applicants to be examined relative to their own peer group. Since the creation of the program, the NIGMS has awarded 231 MIRAs to EIs and 192 MIRAs to ESIs. The MIRA program is especially beneficial for ESIs, as evidenced by the increase in the number of ESI applications from 393 in 2015 (prior to MIRA) to 649 in 2017. The number of ESIs funded by the Institute per year has nearly doubled in the same time period. The NIGMS will continue to monitor the progress and outcomes of the MIRA program as it evolves.

Because some areas of biomedical investigation require groups of investigators to synergistically work together to solve complex problems, the NIGMS recently developed and implemented a new team-science support mechanism known as the Collaborative Program Grant for Multidisciplinary Teams.¹² This investigator-initiated funding opportunity supports multidisciplinary teams of researchers to work toward a shared goal that has the potential to have a major impact on one or more fields of biomedical research. Because this program only funds highly integrated research teams working toward a common objective, it will promote and enable a type of collaborative science that can't easily be supported through other kinds of research grants. Further, these new awards possess an optional component that allows for support of pilot projects by early-stage investigators to develop research in the team's area(s) of expertise with a goal of helping the junior researchers obtain independent funding.

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

The NIGMS plays a leading role in supporting the career development and training of the next generation of scientists, including the development of institutional

¹¹ <https://www.nigms.nih.gov/research/mechanisms/MIRA/pages/default.aspx>.

¹² <https://grants.nih.gov/grants/guide/pa-files/PA-17-340.html>.

research capacities in regions across the country in which the levels of NIH support have been historically low.

Given the rapidly evolving landscape of science and medicine, the Institute is working to catalyze the modernization of graduate education. Recently, the NIGMS issued a new funding opportunity announcement (FOA) for its pre-doctoral T32 training grants¹³ that focuses on addressing several key issues such as: shifting the emphasis from simply teaching scientific “facts” to teaching both scientific and professional skills; developing the acumen needed to become rigorous and responsible scientists; supporting a safe, inclusive and diverse training environment; promoting the use of evidence-based teaching and mentoring practices; and enhancing student career development. Over the next several years, the NIGMS will work to implement this revised T32 program and will carefully evaluate its outcomes. In addition, the NIGMS is also working to ensure that emerging issues can be quickly incorporated and addressed in the training process, as appropriate. For example, the Institute has recently supported the development of open-access curricular training modules in areas related to improving the rigor and reproducibility of biomedical research. These modules are available on the NIGMS website,¹⁴ with more modules due to be added this year. The goal is to generate useful resources for graduate training programs.

Through its Institutional Development Award (IDeA) program, the NIGMS provides targeted support to help broaden the geographic distribution of biomedical research funding by enhancing the competitiveness of investigators located at academic institutions in States having a historically low level of NIH support. The IDeA Centers of Biomedical Research Excellence (COBRE), for instance, support thematic, multidisciplinary centers that expand and develop faculty research capabilities and research infrastructure, in part through the development of core technology facilities needed to carry out modern multidisciplinary collaborative research. Another important aspect of the IDeA program is its support of medical research for rural and underserved communities. The IDeA Clinical and Translational Research Network (CTR), for instance, provides support for clinical and translational research that addresses conditions that have been traditionally higher among certain regions, populations or communities, including (but not restricted to) cancer, cardiovascular disease, and substance abuse disorders.

Because developing a well-trained research workforce begins with early outreach and education, the NIGMS was proud to welcome the NIH Science Education Partnership Awards (SEPA) to the Institute in 2017.¹⁵ SEPA supports diversity in the workforce by providing opportunities for students (specifically at the pre-kindergarten to grade 12 levels) from underserved communities to learn about careers in basic or clinical research. Ten of the fourteen SEPAs in IDeA States are currently in partnerships with IDeA COBREs or IDeA Networks of Biomedical Research Excellence (INBREs). An Institute goal is to fund at least one SEPA in every State.

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

Given that technology plays a critical role in biomedical research, the NIGMS continues to place a high level of significance on supporting the development and dissemination of innovative, new technologies that have the potential to transform research. To this end, the NIGMS supports a multi-phased funding strategy that consists of support for an initial proof-of-concept phase for a given technology followed by potential support for a second prototype refinement phase. These phases can then lead to the adoption and expansion of the technology via commercialization through small business innovation research or small business technology transfer (SBIR/STTR) grants. Technologies can also be applied toward answering specific scientific questions through their incorporation into regular research project grants or, once sufficiently mature, through their incorporation into resources supported by the Institute’s Biomedical Technology Research Resources (BTRR) program.¹⁶ Programs such as the BTRR form an important part of the NIGMS’ portfolio as the Institute seeks to ensure broad access across the research community to cutting-edge technological resources. For example, synchrotron-based technologies, an extremely powerful source of X-rays, are critical for structural biology research; more than 90 percent of all three-dimensional structures of biological molecules in the Protein Data Bank¹⁷ were determined using data from synchrotrons. The NIGMS recently shifted

¹³ <https://grants.nih.gov/grants/guide/pa-files/PAR-17-341.html>.

¹⁴ <https://www.nigms.nih.gov/training/pages/clearinghouse-for-training-modules-to-enhance-data-reproducibility.aspx>.

¹⁵ <https://www.nigms.nih.gov/Research/DRCB/SEPA/Pages/default.aspx>.

¹⁶ <https://publications.nigms.nih.gov/btrrs/searchresults.asp>.

¹⁷ <https://www.rcsb.org/>.

its support for these important resources from research grants to a mechanism focused on user-access, utility and efficiency of operations. A similar model will be used to support the new national cryo-electron microscopy centers.

CONCLUSION

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

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 2019 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH).

COMBATING CHRONIC DISEASE TO IMPROVE HUMAN HEALTH

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

RESEARCH

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

In fiscal year 2019, NIDDK will build upon research accomplishments such as these and upon other research avenues and continue its support for basic studies of both normal and disrupted biological functions and systems. For example, the Re-Building a Kidney (RBK) consortium will continue efforts to enable tissue repair or replacement in kidney disease; already, RBK scientists have found that selecting the proper substrate for growth and structural support is critical to creating blood supply in a "kidney on a chip." Recent studies have shed light on the multiple levels of complex interactions that contribute to how human gut microbes affect health, from molecules produced by the microbes themselves to differences in human diet;

a 2017 workshop on best practices for studies of diet and gut microbiome will help inform rigor and reproducibility in future efforts in this aspect of research on the gut microbiome, which is rapidly emerging as an important contributor to digestive diseases, obesity, nutrition, and many other chronic diseases and conditions.

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

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

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

OTHER

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

is also pursuing multiple efforts to enhance rigor and reproducibility in research. Simultaneously, NIDDK will continue disseminating health and scientific information through multiple venues to educate and inform the public, healthcare providers, and researchers about new developments germane to chronic diseases and conditions.

CONCLUSION

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

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

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

NCI Progress under the 21st Century Cures Act

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

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

A centerpiece of PACT is NCI's \$54 million investment of Cures Act funds across 5 fiscal years to establish four Cancer Immune Monitoring and Analysis Centers and a Cancer Immunologic Data Commons. Together, the centers and data commons will operate as a network to identify mechanisms of response and resistance to cancer therapy and to support adult and pediatric immunotherapy trials.

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

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

Appropriations for Other Cancer Research Priorities

While the 21st Century Cures Act deserves prominence in any discussion of NCI's current cancer research priorities, as a component of our total budget, fiscal year

2017 Cures Act funding represented about 5 percent of NCI's total cancer research appropriation. It is therefore important to emphasize the breadth of other research that NCI's appropriation conducts.

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

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

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

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

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

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

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

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

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

I also want to highlight our progress with the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) Trial and the Pediatric MATCH Trial, two cornerstones

of NCI's Precision Medicine Initiative. Rather than selecting therapies based on where a tumor originated in the body, these trials test the effectiveness of therapies that target specific genetic changes. In 2017, the adult NCI-MATCH Trial achieved its enrollment goal nearly 2 years ahead of schedule. The trial involves more than 6,000 patients from all 50 States at more than 1,000 institutions.

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

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

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

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

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

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

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

EXPLORING NONPHARMACOLOGIC APPROACHES FOR PAIN MANAGEMENT

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

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

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

Based on these and other promising results, NCCIH is leading a new multi-agency partnership between the NIH, Department of Defense (DoD) and Department of Veterans Affairs (VA). This initiative, called the NIH-DoD-VA Pain Management Collaboratory (PMC), addresses the need to focus on “advancing better practices for pain management,” which is outlined in HHS’s five-point strategy to combat the opioid crisis. The PMC will focus on developing, implementing, and testing cost-effective, large-scale, real-world research on nondrug approaches for pain management and related conditions in military and veteran healthcare delivery organizations. The PMC launched in fiscal year 2017 and the agencies plan to fund 11 two-year UG3 (Planning Phase) awards, and up to 10 four-year subsequent UH3 (Implementation Phase) Demonstration Projects, contingent upon successful completion of the short-term pilot and feasibility studies. In addition, a PMC Coordinating Center has been established at Yale University and the Veteran’s Administration Hospital in Connecticut to provide leadership and serve as a resource for the projects by providing innovative tools and best practices. Types of approaches being studied include mindfulness/meditative interventions, movement interventions (e.g., structured exercise, tai chi, yoga), manual therapies (e.g., spinal manipulation, massage, acupuncture), psychological and behavioral interventions (e.g., cognitive behavioral therapy), integrative approaches that involve more than one intervention, and integrated models of multi-modal care. The results of these studies may inform new pain management practices within the DoD and VA and support the use of nondrug approaches for pain management in the general population.

ADVANCING RESEARCH ON NATURAL PRODUCTS

According to the 2012 NHIS, nearly one in five U.S. adults use botanical supplements and other non-vitamin, non-mineral dietary supplements, such as fish oil/omega-3 fatty acids and probiotics. Adverse events related to dietary supplements are estimated to contribute to 23,000 emergency department visits in the U.S. each year. To better inform consumers and their healthcare providers, NCCIH supports rigorous research on the biological mechanisms of the benefits and potential harmful effects of natural products with the goal of improving the body of knowledge available to healthcare providers and patients.

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

In fiscal year 2015, NCCIH partnered with NIH's Office of Dietary Supplements (ODS) to establish the Centers for Advancing Research on Botanical and Other Natural Products (CARBON) Program. Through this program, researchers recently identified two chemicals found in grapes that could significantly reduce depression-like behaviors in mice. The systems targeted by these compounds are not the same as current pharmaceutical antidepressants and may provide novel insights into the biology of depression and could lead to new therapeutic agents. The program is also developing new methods for chemical characterization of natural product mixtures, biological profiling assays, and creating new informatic tools to rigorously analyze and share data.

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

CONCLUSION

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

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

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

FIFTY YEARS OF VISION RESEARCH

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

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

In its early years, NEI pioneered new methodology for conducting placebo-controlled, multi-center clinical trials, which led to vision-saving laser surgery to treat diabetic retinopathy, AMD, and glaucoma. Large trials identified dietary supple-

ments demonstrated to slow progression to end-stage AMD. Trials compared effectiveness of different therapies for AMD, diabetic retinopathy, and an inflammatory eye condition called uveitis, to inform patients and their doctors of options for personalized treatment. Elevated fluid pressure in the eye, called ocular hypertension, is a precursor for glaucoma, especially in African Americans who have a disproportionate burden of this disease. 1,500 patients participated in the Ocular Hypertension Treatment Study, including 400 African American participants, which led to new treatment guidelines that can reduce incidence in African Americans by 50 percent. A 20-year follow-up study is currently underway to assess the long-term impact. More recently, the first application of genomics methods led NEI scientists to uncover new genetic components for AMD, opening the door to new treatments. Before NEI was established, a major cause of lifelong blindness was retinopathy-of-prematurity (ROP), a disease caused by abnormal development of retinal blood vessels in low birth weight babies born very prematurely. Technology to identify and treat ROP has improved dramatically over the years and a recent NEI trial demonstrated that premature infants can be screened for ROP remotely via telemedicine, expanding access to specialists in rural and underserved communities.

RECENT PROGRESS IN VISION RESEARCH

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

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

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

SEEING INTO THE FUTURE

The NEI Audacious Goals Initiative (AGI) seeks to restore vision through neuroregeneration in the eye and visual system. This fundamental regenerative medicine approach was initiated in 2013 and is advancing rapidly. NEI has established two collaborative consortia of research teams working on different facets of the challenge: one on functional imaging, and a second for discovery science to identify new regeneration factors by looking in model systems. For example, unlike adult mammals, zebrafish can regenerate their retina after injury, which led NEI researchers to identify a key regeneration factor, present in newborn mice, and through manipulating this factor, they caused new neurons to form in adult mice. Scientists also found that exosomes secreted from stem cells protect a type of retinal cells, the ganglion cells, which are damaged by glaucoma. Exosomes are now being examined for potential therapeutic effect. Exosome-treated rats lost only a third of their retinal ganglion cells following optic nerve injury, compared with 90 percent loss in untreated rats. NEI is now reviewing proposals for a third AGI consortium, to develop animal model systems to facilitate translation of discovery research into the clinic.

NEI just launched new stem cell trials for retinal vein occlusion (RVO)—the second leading retinal vascular cause of vision loss after diabetic retinopathy, and for limbal stem cell deficiency (LSCD). In RVO, the vessels draining blood from retinal tissue become clotted, leading to leaking and bleeding and ultimately starving the neurons of oxygen. The trial will test the safety, feasibility and efficacy of injecting stem cells derived from the patient's own bone marrow into their eyes. Corneal limbal cells, are responsible for renewing the front layer of the transparent cornea. In thousands of patients with LSCD, loss of these cells causes visual impairment from chronic inflammation, abnormal blood vessel growth, and opaque corneas. The 21st Century Cures Act Regenerative Medicine Program is supporting an NEI project to treat LSCD. Researchers identified a limbal cell marker, ABCB5, which has allowed them to isolate, purify and expand limbal stem cells in the lab in sufficient quantities for transplantation. This summer, NEI scientists are about to launch the first clinical trial using induced pluripotent stem cells-derived retinal tissue to treat the dry form of AMD. Skin cells taken from AMD patients will be manipulated in the lab for about 3 months, then transplanted back into the same patients, thereby minimizing rejection of foreign tissue that affects many types of transplant therapies.

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

In January, NEI announced the launch of a new strategic planning process, under the auspices of the National Eye Advisory Council. The 5-year plan will be developed with significant community input, centered around scientific program working groups. It will also align with the NIH Strategic Plan and requirements laid out in the 21st Century Cures Act, including research to address health disparities.

PREPARED STATEMENT OF MARTHA J. SOMERMAN, DDS, 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 2019 budget request for the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH).

The mission of NIDCR is to improve dental, oral, and craniofacial health through research, research training, and the dissemination of health information. A recent study looking at personal healthcare spending in the United States by condition estimates that Americans spend \$66.4 billion annually on the treatment of oral disorders and another \$48.7 billion for general dental care and preventive services. Together, the total surpasses the costs of treatment related to a common condition among Americans—diabetes—by more than \$13 billion.¹⁸ NIDCR leads the effort to reduce this burden by supporting basic, translational, and clinical research and research training to improve dental, oral, and craniofacial health. By promoting the timely translation of those findings into practice NIDCR helps advance treatment and prevention strategies for all Americans.

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

PIONEERING A GENE THERAPY TO TREAT CHRONIC DRY MOUTH

For most people who survive head and neck cancers, successful treatment with radiation therapy comes at a high price—significant loss of salivary gland function, leading to chronic dry mouth and its adverse health effects. Radiation therapy works by killing malignant tumor cells, but it does not discriminate among cell

¹⁸ Dieleman J. US Spending on Personal Health Care and Public Health, 1996–2013. JAMA. 2016; 316(24):2627–2646.

types. It also kills saliva-producing cells, which causes saliva production to shut down. This can lead to problems chewing, tasting, talking, and swallowing food, and significantly increases the risks for dental decay, tooth loss, and oral infections. NIDCR supports research to unravel the complex molecular and cellular processes involved in salivary gland function and fluid secretion. These investments have inspired the development of a gene therapy to treat chronic dry mouth caused by radiation treatment. The therapy delivers specific DNA sequences into the surviving salivary gland cells, resulting in the production of specialized tube-shaped proteins called aquaporins, which allow water to flow out of the salivary gland cells. Studies in mouse models showed that the gene therapy generated enough aquaporin proteins to restore salivary flow. This research led to a clinical trial conducted on the NIH campus that is currently recruiting patients to test the gene therapy treatment in people whose salivary glands have been damaged by radiation therapy for head and neck cancer. Results from the first phase of the study are encouraging and suggest that this approach could be a promising treatment. Building on these studies, another clinical trial is being planned to see if the therapy can also be used to restore salivary function in individuals whose chronic dry mouth is caused by Sjögren's syndrome, an autoimmune disorder that damages salivary glands.

DEVELOPING INNOVATIVE TECHNIQUES TO ADVANCE REGENERATIVE MEDICINE

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

FINDING PAIN RELIEF IN UNEXPECTED PLACES

Chronic pain is a major health problem that affects almost one-quarter of the U.S. population.¹⁹ Opioids are often prescribed to alleviate chronic pain, although they carry a strong risk for addiction. Identifying new effective and non-addictive pain treatments remains a priority for NIDCR, especially in regard to TMD, a group of conditions that can cause severe and chronic pain in the jaw and muscles of the head and neck. In 2005, NIDCR launched OPPERA (Orofacial Pain, Prospective Evaluation and Risk Assessment)—a multi-site population-based study—to identify the biopsychosocial and genetic risk factors that cause TMD. Early OPPERA studies found an association between the gene for epidermal growth factor (EGFR) and the development of chronic pain in patients with TMD. Drugs that block the activity of EGFR are currently being used to inhibit tumor growth in some types of cancer. Strikingly, there have been case reports of cancer patients reporting a significant reduction in pain when treated with EGFR-blocking drugs. Taking these observations into the laboratory, NIDCR-funded investigators used a mouse model to show that EGFR-blocking drugs alleviate inflammatory and neuropathic pain. These drugs function by blocking the activity of EGFR in neurons that receive and interpret sensory stimuli—such as pain—in the body. This intriguing finding could lead to the development of more effective treatments for chronic pain that also reduce the risks for addiction.

¹⁹Gereau RW, et al. A pain research agenda for the 21st century. *J Pain*. 2014; 15(12):1203–1214.

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

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

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 2019 budget request for the National Institute on Minority Health and Health Minorities of the National Institutes of Health (NIH).

ADVANCING THE SCIENCE OF MINORITY HEALTH AND HEALTH DISPARITIES RESEARCH

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

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

RESEARCH

Advancing the science of minority health and health disparities requires scientific vision; that means building and developing evidence-based information that takes

into account the social determinants of health and the places where we live, learn, work, and play. To meet the demands of keeping up with biomedical advances, NIMHD is strengthening research in minority health and health disparities; increasing opportunities for investigator-initiated research; strengthening the evaluation and reporting of minority health and health disparities research; and supporting the expansion of workforce diversity.

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

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

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

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

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

BUILDING A DIVERSE BIOMEDICAL WORKFORCE

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

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

CONCLUSION

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

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

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

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

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

DIVISION OF PROGRAM COORDINATION, PLANNING, AND STRATEGIC INITIATIVES

DPCPSI (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, and research infrastructure. DPCPSI serves as a resource for the ICs and OD for portfolio analysis by developing, using, and disseminating data-driven approaches and computational tools. DPCPSI serves as the focal point for coordinating research to advance the health and wellbeing of sexual and gender minorities and for American Indians and Alaska Natives, and coordinating tribal consultation activities for the NIH.

The Office of Research Infrastructure Program (ORIP) provides support for research into model systems of human diseases and a variety of research infrastructure needs. ORIP supports a number of repositories of animal models, biological materials, genetic stocks, and human biospecimens. ORIP also makes grant awards to fund the purchase of expensive state-of-the-art scientific instruments and to update animal research facilities. ORIP supports training and career development for veterinarian-scientists engaged in biomedical research and contributing to interdisciplinary research teams addressing topics at the intersection of human/animal populations and the environment.

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

The Office of Behavioral and Social Sciences Research (OBSSR) furthers the mission of the NIH by emphasizing the critical role that behavioral and social factors play in health, 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.

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

The Office of Disease Prevention (ODP) is responsible for assessing, facilitating, and stimulating research in disease prevention and health promotion, and disseminating the results of this research to improve public health. In fiscal year 2019, ODP will release a new strategic plan which outlines the priorities that the Office will focus on over the next 5 years and highlights ODP's role in advancing prevention research at the NIH. The Office of Dietary Supplements (ODS) is within the ODP organizational structure. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

The Office of Strategic Coordination (OSC) and the Common Fund (CF)- OSC manages the Common Fund (CF), which functions as a "venture capital" space where high-risk, innovative endeavors with the potential for extraordinary impact can be supported. CF supports approximately 30 programs that focus on areas of emerging scientific opportunities, rising public health challenges, and knowledge gaps that deserve special emphasis; that would benefit from strategic coordination and planning across NIH Institutes and Centers (ICs); and that are designed to address specific, high-impact goals and milestones within a 5- to 10-year timeframe.

Collectively, these programs represent strategic investments aimed at solving problems or building resources to affect research throughout the entire biomedical research enterprise. Most CF programs consist of a series of integrated initiatives that collectively address a set of goals aiming to transform the way research is conducted, the way that health and disease are understood, and/or the way that diseases are diagnosed or treated.

ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES

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

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

ALL OF US RESEARCH PROGRAM

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

Since July 2016, All of Us achieved several key implementation milestones, including initial study protocol approval, establishment of a state-of-the-art biobank to process and store biological samples from patients, and construction of a big data IT system to store data for research purposes. Working together with a consortium of Federal, academic, and industry partners, All of Us began participant enrollment for its beta testing phase in May 2017, and, as of March 25, 2018, more than 35,000 participants are currently enrolled, of whom over 20,000 have completed the full protocol.

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

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

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

DRUG USE AND ADDICTION RESEARCH PRIORITIES

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

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

include the disconcerting rise in fatalities associated with cocaine and methamphetamine use, as well as the rise of new synthetic drugs and delivery systems, such as e-cigarettes, that are changing how people perceive and use drugs.

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

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

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

RESEARCH HIGHLIGHTS

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

OPIOID CRISIS

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

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

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

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

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

medications to treat pain including the potential for developing an opioid pain medication devoid of addictive effects.

ADOLESCENT DRUG USE AND BRAIN DEVELOPMENT

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

PREVENTION AND TREATMENT

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

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

The NIDA Clinical Trials Network (CTN) is a collaborative partnership with clinicians, researchers, and participating patients that cooperatively develops, tests, and delivers new treatment options to patients with SUD including opioid addiction. The CTN studies behavioral, pharmacological, and integrated treatment interventions in rigorous, multisite clinical trials across a network of community-based treatment settings. Current CTN-funded trials include studies on how to implement buprenorphine in emergency departments and by primary care physicians, engagement of pharmacists for prescribing and monitoring buprenorphine to patients with an OUD and the effectiveness of a combination pharmacotherapy regimen to treat methamphetamine use disorder, among others.

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

impact of prefrontal cortex deficits caused by cocaine or heroin use and to develop clinically useful indicators (biomarkers) of addiction severity or treatment efficacy that will support the development of more effective treatments.

CONCLUSION

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