

**PRIORITIZING CURES:
SCIENCE AND STEWARDSHIP AT
THE NATIONAL INSTITUTES OF HEALTH**

HEARING
OF THE
**COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS**
UNITED STATES SENATE
ONE HUNDRED FIFTEENTH CONGRESS
SECOND SESSION
ON
EXAMINING PRIORITIZING CURES, FOCUSING ON SCIENCE AND
STEWARDSHIP AT THE NATIONAL INSTITUTES OF HEALTH

AUGUST 23, 2018

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C O N T E N T S

STATEMENTS

THURSDAY, AUGUST 23, 2018

Page

COMMITTEE MEMBERS

Alexander, Hon. Lamar, Chairman, Committee on Health, Education, Labor, and Pensions, Opening statement	1
Bennet, Hon. Michael F., a U.S. Senator from the State of Colorado, Opening statement	4

WITNESSES

Collins, Francis, M.D., Ph.D., Director, National Institutes of Health, Be- thesda, MD	5
Prepared statement	8
Bianchi, Diana, M.D., Director, National Institute of Child Health and Human Development, Bethesda, MD	14
Fauci, Anthony, M.D., Director, National Institute of Allergy and Infectious Diseases, Bethesda, MD	31
Hodes, Richard, M.D., Director, National Institute on Aging, Bethesda, MD	23
Sharpless, Ned, M.D., Director, National Cancer Institute, Bethesda, MD	29

QUESTIONS AND ANSWERS

Response by Francis Collins to questions of:	
Senator Alexander	34
Senator Roberts	37
Senator Young	42
Senator Enzi	44
Senator Collins	45
Senator Burr	49
Senator Murray	52
Senator Casey	73
Senator Baldwin	76
Senator Warren	77
Senator Kaine	79
Senator Smith	80
Senator Jones	81

**PRIORITIZING CURES:
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Thursday, August 23, 2018

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The Committee met, pursuant to notice, at 10:02 a.m. in room SD-430, Dirksen Senate Office Building, Hon. Lamar Alexander, Chairman of the Committee, presiding.

Present: Senators Alexander [presiding], Isakson, Collins, Cassidy, Scott, Murray, Casey, Bennet, Murphy, Warren, Kaine, Hassan, Smith, and Jones.

OPENING STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. The Senate Committee on Health, Education, Labor, and Pensions will please come to order.

Senator Bennet and I will each have an opening statement, and then I will introduce our witness, National Institutes of Health Director, Francis Collins. Then we will hear from Dr. Collins, and Senators will each have 5 minutes to ask questions.

We have a vote at 10:30, not in the Committee but on the floor, and so we will continue straight through with the questioning. Senator Bennet, and I, and other Senators will share the presiding today so that we can continue the discussion.

Not long ago, I ran into a friend from Vanderbilt University who is perhaps our largest contributor to cancer research there. This is what he said to me, "Is it not a shame that the Congress is not doing anything to fund biomedical research?"

[Laughter.]

The CHAIRMAN. This is how I replied to him. I said, "In December 2016, Congress passed what Senator McConnell called, 'The most important legislation of the year,' the 21st Century Cures Act. That Act gave the National Institutes of Health \$4.8 billion for the Precision Medicine Initiative, the BRAIN Initiative, the Cancer Moonshot, regenerative medicine, as well as many new flexibilities and authorities to conduct the research that we hope will lead to breathtaking new medicines, treatments, and cures."

That was thanks to Senator Blunt, Senator Murray, Senator Durbin, Senator Moran, and many other Senators. The Appropriations Committee is on track to provide record funding for the fourth year in a row to the National Institutes of Health.

First, Congress increased N.I.H. funding by \$2 billion in 2015; that is in addition to the Cures money. Then, we increased N.I.H. funding by \$2 billion more in 2016. Then in 2017, Congress increased funding for the National Institutes of Health by \$3 billion, including \$500 million to work on a non-addictive painkiller. And today, we expect the full Senate to approve an additional \$2 billion increase to N.I.H. funding for next year.

This means, if the bill we hope the Senate approves today is signed into law, Congress will have increased funding for the National Institutes of Health by \$9 billion since 2015, a 30 percent increase.

The way we do our budgets here, that usually builds into the budgets over a longer period of time, that money, as a base. So if you counted over ten years, a \$2 billion increase in one year means over ten years \$20 billion in new spending authority. These increases have included the funding we intended to deliver on Cures.

The purpose of this hearing is to make sure that money is being spent wisely.

The reason Congress has devoted so much funding to biomedical research is well-captured in testimony that Dr. Collins gave before the Appropriations Committee a couple of years ago, when he offered ten “bold predictions,” as you called them then, Dr. Collins, of what we might be able to achieve in the next ten years if we continued to invest in research as we now have.

Some of these predictions that you made then were:

Being able to identify Alzheimer’s disease before symptoms appear;

The possibility we could rebuild a patient’s heart with their own cells;

The creation of a safe and effective artificial pancreas, making life easier and healthier for the millions of Americans with diabetes;

Development of new vaccines, including for Zika and HIV/AIDS, and the universal flu;

Development of a new, non-addictive pain medicine, which may be “the Holy Grail” to dealing with the opioid crisis;

Significant progress on the Precision Medicine Initiative, which aims to map the genomes of one million volunteers so we can better tailor treatments to individual patients; and,

New treatments for cancer patients.

Those are all the bold predictions.

The two things I hope we keep in mind when we look at these large increases in funding that Congress has given the National Institutes of Health in recent years is first, it is hard to think of a major scientific advancement since World War II that has not been supported by Federal research funding. But we are not the only country that has figured that out. Other countries have seen that investments in basic research can lead to breathtaking new discoveries.

Since 2007, China has increased its spending on basic science by a factor of four and may surpass the United States in total spending on research and development this year, according to Norm Augustine, who, during the George W. Bush administration, chaired the Rising Above the Gathering Storm group, the bipartisan com-

mittee that was charged with making recommendations about how to keep America's competitive advantage.

The second thing I hope we keep in mind is that these large increases in funding for biomedical research, and other increases for national laboratories and other basic research, are not the part of the Federal budget that creates the huge national deficit.

This spending, the spending we are talking about here, is part of the so-called discretionary spending, which is now roughly 29 percent of all Federal spending and includes the national defense, the national parks, the national laboratories, the National Institutes of Health among other things.

Over the last ten years, this is the part of the budget that has grown at about the rate of inflation. Over the next ten years, according to the Congressional Budget Office, it is expected to grow at only a little more than the rate of inflation. So funding for research has been carved out of these budget limitations and is not the reason for the increasing Federal debt.

What causes the Federal debt to increase is spending on entitlements, which according to the CBO, is going to squeeze funding for research, our national labs, and our national security over the next ten years.

I have one other topic, Dr. Collins, I want to give you an opportunity to discuss.

You recently told Senator Murray and me about an ongoing investigation into federally funded research, including, in some cases, research conducted by foreign nationals. I would ask you to take a few extra minutes in your opening presentation to brief the Committee on this issue. It is important to protect the integrity of research funded by the Federal Government.

It is also important to recognize the role that scientists from other countries have played in research funded by the U.S. Government.

For example, the director of Oak Ridge National Laboratory came to this country from India, before he became a citizen. The incoming director of the Los Alamos Laboratory came from Canada, before he became a citizen. The director of the National Renewable Energy Laboratory came from Germany before he became a citizen.

Many graduate students at American universities, who work on N.I.H. grants, are foreign nationals legally in our country. And since 2000, thirty-three Americans, who were born in other countries, have won Nobel Prizes in Chemistry, Medicine, and Physics.

I want to acknowledge the great advantage to our country of attracting the brightest people from around the world to our universities and laboratories as long as they follow the rules and conduct their research in appropriate ways.

This is an issue that impacts more than just the National Institutes of Health and more than just this Committee's jurisdiction. But if there are some bad actors who are attempting to influence N.I.H.-funded research, we want to know about it, and we want to know what authority you need, or others need, to deal with it.

Thank you.

Senator Bennet.

OPENING STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Chairman Alexander, for holding this bipartisan hearing on N.I.H.'s important work, including the agency's progress in implementing the 21st Century Cures Act.

Dr. Collins, thank you for being here today and for your colleagues taking the time to be here to give us an update.

In the last few decades, we have seen exponential advancements in medical research. The research community has developed cures and maintenance treatments for serious illnesses that used to be a death sentence.

When I worked on the Breakthrough Therapies Act with Senators Burr and Hatch in 2012, we recognized the need to expedite treatments when early trials showed promises for conditions within an unmet need.

We had no idea how successful the program would be. As of August 13, the FDA has approved 116 breakthrough therapy designated products. Many of these treatments show the promise of precision medicine.

As N.I.H.-supported research has made clear, therapies that target specific genes or molecular pathways make it possible for providers to predict whether patients will respond to certain treatments.

This Committee also recently worked to pass the RACE for Children bill to ensure that kids with cancer have the same access to targeted treatments that adults do. Pediatric oncologists at Children's Hospital Colorado are hopeful that they can launch as many as twenty-five new clinical trials because of the new law.

These treatments will come from the research bench to the bedside, in large part, because of the great work happening at N.I.H. today.

The 21st Century Cures Act included monumental policies to advance medical research. The hope of personalized medicine has already been a reality for some patients. I am looking forward to hearing more from Dr. Collins about the Precision Medicine Initiative and how we can reach even more Americans with therapies that maximize benefits and minimize toxic side effects.

The 21st Century Cures Act also included the BRAIN Initiative, which will help researchers and the medical community grasp the intricacies of the human brain.

Though we have gained a better understanding of how to treat different types of cancers or cystic fibrosis, the development of meaningful therapies for neurological diseases like Alzheimer's, Parkinson's, and ALS have lagged behind. I look forward to hearing about the progress on these initiatives.

I am also interested to hear more about the work N.I.H. is doing to combat the opioid crisis, which continues to rip apart families and take lives in Colorado and across our country. This Committee has been active in working on an approach as a first step to respond to this epidemic, but there is so much more to do.

With over 42,000 lives lost in 2016, and a preliminary estimate of almost 50,000 Americans in 2017, we still have much more to do.

I want to thank the Chairman for raising the role of talent programs, and I am interested in hearing what you have to say on this subject, Dr. Collins. I would like to echo what the Chairman stated.

Breakthroughs in medical research cannot happen in the silo of any one country, but we also want to ensure that we prioritize transparency and appropriately deal with bad actors who are taking steps that actually undermine the science and American efforts to do research.

Thanks again to the Chairman, and the Ranking Member, and to Dr. Collins for being here today. I look forward to your testimony.

The CHAIRMAN. Thank you, Senator Bennet.

I am pleased to welcome Dr. Collins to today's hearing. Thanks to him for being here. He is overseeing the work of the largest supporter of biomedical research in the world. He has been the Director of N.I.H. since 2009.

He is accompanied by Dr. Diana W. Bianchi, Director of the National Institute of Child Health and Human Development; Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases; Dr. Richard Hodes is Director of the National Institute on Aging; and Dr. Ned Sharpless, Director of the National Cancer Institute.

We welcome Dr. Collins. Please give your testimony now.

**STATEMENT OF FRANCIS S. COLLINS, M.D., Ph.D., DIRECTOR,
NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND**

Dr. COLLINS. Chairman Alexander, Senator Bennet, and Members of the Senate HELP Committee.

Thank you for giving me a little extra time to speak on this issue of protecting the integrity of U.S. biomedical research from undue foreign influence, which both of you have raised.

N.I.H. is built on the bedrock principles of scientific excellence, unassailable integrity, and fair competition. N.I.H.'s commitment to these principles is unwavering.

We have long understood, however, that the robustness of the biomedical research enterprise is under constant threat by risks to the security of intellectual property and the integrity of peer review. This knowledge has shaped our existing policies and practices.

But through our own investigations, conversations with law enforcement, and even just from watching the press, we can see that the magnitude of these risks is increasing.

Yesterday, I wrote to the senior representatives of more than 10,000 N.I.H. grantee institutions to request that they review their records for evidence of malfeasance in three areas of concern.

First, failure by some researchers at N.I.H.-funded institutions to disclose substantial contributions of resources from other organizations including foreign governments, which threatens to distort decisions about the appropriate use of N.I.H. funds.

Second, diversion of intellectual property; in grant applications or produced by N.I.H. supported biomedical research to other entities, including other countries.

Third, is failure by some peer reviewers to keep information on grant applications confidential including, in some instances, disclo-

sure to foreign entities or other attempts to influence funding decisions.

While we, at N.I.H., depend on the major security agencies, and the Department of Health and Human Services's broader national security efforts, to protect our interests, N.I.H. and the U.S. biomedical research community at large have a vested interest in mitigating these unacceptable breaches of trust and confidentiality that could undermine the integrity of U.S. biomedical research.

To help address this challenge, I am today announcing the new Working Group of my Advisory Committee to the director whose charge will be to identify robust methods to, first, improve accurate reporting of all sources of research support, financial interests, and affiliations.

Second, mitigate the risk to intellectual property security.

Third, explore additional steps to protect the integrity of peer review.

But fourth, and importantly, to carry out these actions in a way that reflects the long tradition of partnership between N.I.H. and grantee institutions, and that emphasizes the compelling value of ongoing honorable participation by foreign nationals in the American scientific enterprise, which both of you have already highlighted in your opening statements.

President M. Roy Wilson of Wayne State University and Dr. Lawrence Tabak, my principal deputy, will co-chair this group. The other members include President Jeffrey Balser of Vanderbilt University, President Ana Mari Cauce of the University of Washington, President Michael Drake of Ohio State University, President Wallace Loh of the University of Maryland, President Samuel Stanley of Stony Brook University, and Dr. Maria Zuber, Vice President for Research at M.I.T.

The U.S. biomedical research enterprise is the envy of the world for the excellence of our discovery and innovation. Our leadership is made possible because the overwhelming majority of researchers participating on N.I.H. grants, whether U.S. or foreign born, are honest, hardworking contributors to the advancement of knowledge that benefits us all.

We must move effectively to root out examples where our system is being exploited, but make sure to preserve the vibrancy of a diverse workforce that has played a major role in the American biomedical research success story.

But just like in sports, it takes more than a good defense to win at science. It also takes a strong and talented offense. So if you will allow me for the rest of my testimony, I would like to focus on the 21st Century Cures Act and many other proactive ways in which you and your colleagues are helping to bolster N.I.H.'s tradition of success.

I spend a lot of time with early stage researchers. Wherever I go, I set aside time to hear directly from them about their dreams, their ideas and, yes, their concerns. I know you, too, have met many of them both in your home states and on your much appreciated visits to N.I.H.

I think it is critical that we all ask ourselves, 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?

I believe the answers could be said to lie in certain key areas that we could call the five keys to success in science today. They are: a stable trajectory of support; a vibrant workforce; computational power; new technologies and facilities; and most of all, scientific inspiration.

The good news is that thanks to you—Mr. Chairman, you have outlined what has happened in the last three years and perhaps the fourth year about to happen—early stage researchers are now seeing a stable trajectory of support. That provides such an encouragement to tackle difficult, challenging, high risk projects.

Your work over the last three years is helping us to begin to reverse a distressing decade long decline in N.I.H.'s purchasing power for research, which is carried out in every state of the Nation.

This year, we expect at the end of Fiscal Year 2018 to fund more than 11,000 new and competing grants; the largest number in history. The 21st Century Cures with its total funding of \$4.8 billion over ten years for four signature initiatives is a critical part of this.

A second key to success is a vibrant workforce. 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 have a look at a new metric that we are using to evaluate success.

This shows the trend in the number of individual principal investigators supported by N.I.H. over the past fifteen years. As you can see, that number is once again growing nicely. Note the surge that occurs around 2016, a surge that reflects when Congress began to change the trajectory of N.I.H. support and shows how that investment is paying off.

The third key to success is computational power. This probably would not have been on my short list in 2009 when I started as N.I.H. Director, but 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 supported through 21st Century Cures, has created new imaging tools that are turning out droves of amazing data. And there is also data generated by structural biology, and the microbiome and the All of Us Research Program are part of the Precision Medicine Initiative, also supported by the Cures Act.

On May 6, all of us began enrolling one million people living in the United States. Today, we are going to hit the 100,000 mark for volunteers. Nearly half of those are from communities historically underrepresented in medical research, providing a great opportunity to look at health disparity.

To realize the full potential of these and other resources, we must also develop new technologies and facilities. Quite often, it is the technology itself that is 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 a patient's body using technology to reengineer those cells and then returning them to the patient.

Many of our labs are not currently set up to handle these highly individualized processes, so it is crucial we make upgrades to keep pace.

But now, onto my favorite: scientific inspiration. I can assure you that N.I.H.-funded researchers come to work every day full of innovative ideas and the wherewithal to see those ideas through, thanks to the Congress. Let me share just one example that really fits with the theme of this hearing, which is prioritizing cures.

More than a decade ago, N.I.H. launched a special project on Spinal Muscular Atrophy, SMA, a tragic, inherited disease. As you see here, in its most severe form, it leaves babies floppy, unable to hold their heads up, feed well, and eventually even to breathe. Nearly all are deceased by fifteen months.

Ten years ago, there was no treatment, but researchers had just discovered the DNA mutations that caused SMA. So N.I.H. 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 for SMA in fifteen infants with severe disease. Again, these are infants not expected to survive more than fifteen months.

They infused a viral vector designed to deliver the normal gene to the spinal cord, which is where the problem is and held their breath. Over the next few months, something truly dramatic happened.

Like Evelyn Villarreal, who you see in this picture with her parents, 100 percent of the kids who got the highest dose of gene therapy were alive at twenty months. Nearly all could talk and feed themselves. And some, like Evelyn who is now three-and-a-half, not only can talk and walk, but she can even do pushups. Check out this video.

[Video presentation.]

Dr. COLLINS. I am very happy that Evelyn, her mom Elena, and her dad Milan, are here with us this morning. So please stand up, if you would, and say hello to the Members of the Committee.

[Applause.]

Dr. COLLINS. Evelyn, do you think you could do a twirl for us? I saw one earlier that looked pretty good; maybe a little too many witnesses. Well, does that not warm your heart?

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

We are the National Institutes of Health. But for many, like the Villarreal family, we are also the National Institutes of Hope.

Thank you and we look forward to your questions.

[The prepared statement of Dr. Collins follows:]

PREPARED STATEMENT OF FRANCIS S. COLLINS

Good morning, Chairman Alexander, Ranking Member Murray, and distinguished Members of the Committee. 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 Committee for your sustained commitment to NIH to ensure that our Nation remains the global leader in biomedical research and advances in human health.

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.

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. NIH is developing evidence-based, data-driven strategies to assure that NIH investments are directed in ways that maximize scientific output. We are being aided in these efforts by an expert Working Group of the Advisory Committee to the Director, who will present recommendations in December 2018. But several important steps are already being taken: Institutes and Centers are placing greater emphasis on current NIH funding programs to identify, grow, and retain new and early career investigators across these critical career stages. The Office of the Director is tracking progress across NIH in order to assess if these strategies are working. NIH remains committed to the development, support, and retention of our next generation of investigators.

NIH is also committed to funding the highest priority scientific discoveries while also maintaining fiscal stewardship of Federal resources. 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 NIH supports across the Institutes and Centers.

The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative is revolutionizing our understanding of the human brain, the most complex structure in the known universe. Launched in 2013, this large-scale effort is pushing the boundaries of neuroscience research. Ultimately, these insights will have profound consequences for the prevention or treatment of a wide variety of brain disorders. By accelerating the development and application of innovative technologies, researchers are producing a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. This picture is filling major gaps in our current knowledge and providing unprecedented opportunities for exploring exactly how the brain enables the human body to record, process, utilize, store, and retrieve vast quantities of information, all at the speed of thought.

This year, the BRAIN Initiative will support critical areas including data infrastructure and sharing, the BRAIN Initiative Cell Census Network (which is developing an atlas of brain cell types), the Team Research Brain Circuits Program, and human brain studies. In human studies, the BRAIN Initiative is advancing brain imaging and non-invasive brain stimulation, and public private partnerships are investigating self-adjusting implanted brain stimulation therapies that are already showing promise. Ultimately, this will lead to an increased understanding of brain health, and a means of preventing brain disorders such as Alzheimer's disease, Parkinson's, schizophrenia, autism, and drug addiction.

In April 2018, NIH launched the HEAL (Helping to End Addiction Long-term) Initiative, an aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. NIH has and will continue to support cutting-edge research on new treatments for the millions of Americans with opioid addiction, and for the millions more with daily chronic pain. Both pain and addiction are complex neurological conditions, driven by many different biological, environmental, social, and developmental contributors. To build on this understanding, 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 study; develop new non-addictive treatments for pain through the study of novel targets and biomarkers; and build a new clinical trials network focused on pain. NIH, in partnership with the Substance Abuse and Mental Health Services Administration (SAMHSA), will also study how effective strategies for opioid addiction and overdose reversal can be put into practice in places severely affected by the opioids crisis through the HEALing Communities study. Thanks to your support, all hands are on deck at NIH for this public health crisis.

Another exciting area of continued investment is in cancer immunotherapy, in which a person's own immune system is taught to recognize and attack cancer cells. After years of research supported by NIH, immunotherapy is leading to cures of some cancers like leukemia, lymphoma, and melanoma.

But other cancers, particularly solid tumors like colon, pancreas, breast, and prostate, have proven much less responsive. I am excited to tell you that some of those barriers may be ready to come down. Just last month, a team led by NIH's Dr. Steve Rosenberg announced a novel modification of an immunotherapy approach that led to a complete regression, most likely a cure, of widely metastatic breast cancer in a woman with this previously fatal form of the disease. As always, I must counsel patience—this immunotherapy success story for solid tumors involves very few cases right now, and must be replicated in further studies. But, without doubt, this woman's life-saving experience represents hope for millions more. As exciting as potential cures like this can be, NIH is focused on advancing not just cancer therapies, but also cancer care. I would like to tell you about an NIH-funded trial that beautifully illustrates the progress we are making in this area.

Each year, as many as 135,000 American women who have undergone surgery for the most common form of early stage breast cancer face a difficult decision: whether or not to undergo chemotherapy to improve their odds. Now, thanks to a large, NIH-funded clinical trial, called TAILORx, we finally have some answers. It turns out about 70 percent of such women actually do not benefit from chemotherapy, and a genomic test of tumor tissue can identify them quite reliably. Clearly, it is best to spare women from the potentially toxic side effects of these drugs, if at all possible. Furthermore, the ability to limit the use of chemotherapy to the 30 percent of women who will really benefit can yield significant cost savings for our health-care system, as much as \$1.5 billion a year.

Indeed, figuring out what health approaches work best for each individual—and why—is the goal of another important NIH Initiative: the Precision Medicine Initiative (PMI). Precision medicine is a revolutionary approach for disease prevention and treatment that takes into account individual differences in lifestyle, environment, and biology. While some applications of precision medicine have found their way into practice over the years, this individualized approach is simply not available for most diseases. The *All of Us* Research Program, a key component of PMI, is building a national resource—one of the world's largest, most diverse biomedical data sets in history—to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care. *All of Us* will enroll one million or more U.S. volunteers from all life stages, health statuses, races/ethnicities, and geographic regions to reflect the country's diverse places and people to contribute their health data over many years to improve health outcomes, fuel the development of new treatments for disease, and catalyze a new era of evidence-based and more precise preventive care and medical treatment.

Across the Nation, NIH has engaged ten large health provider organizations, six community health centers, and the Department of Veterans Affairs to be our partners in this ambitious study. The program has funded over thirty community partner organizations to motivate diverse communities to join and remain in the program, with a focus on those traditionally underrepresented in biomedical research.

We began a robust, year-long beta testing phase in May 2017, during which each of our partners were able to test their systems and processes to ensure a good experience for participants and ensure that the security of the data systems was of the highest possible order. I am happy to tell you that *All of Us* launched nationally on May 6, 2018 with events across the country to mark the program's open enrollment. As of August 15, 2018, almost 100,000 individuals have started the enrollment process, and over 50,000 have completed all the steps in the protocol. Of those almost 50 percent are from racial and ethnic groups who have been historically underrepresented in biomedical research.

Following the national launch, we continue to improve and adjust the program based on participant feedback and emerging scientific opportunities and technological advances. We also are currently building the *All of Us* data resource, which is designed to be used by a broad range of researchers to study complex risk factors, support ancillary studies and clinical trials, and link to other large data sets. *All of Us* will be critical to realizing the promise of personalized medicine.

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. I look forward to answering your questions.

The CHAIRMAN. Thank you.

We will begin a round of five minute questions. As I mentioned earlier, we have a vote in a few minutes, but we will continue right through that, and pass the presiding responsibility around.

First, to Evelyn and to her parents, thank you so much for coming. It is a wonderful story, and that is the reason we are so interested in the work that Dr. Collins and his associates do.

Thanks to Dr. Collins's team for being here.

Dr. Collins, let me ask you to talk a little more about some areas you mentioned. With all this new money, and it is a lot, a 30 percent increase in a short amount of time, there are three areas that, in my conversations with researchers around the country, they suggest that we could do a better job of, and maybe you already are and we just do not know about it. So let me tell you about those three areas and see what you say.

Number one, support more young scientists. Now, you talked about it there. But the feeling is if whatever money, even if it is a lot of money is available only to the established figures, that it discourages the brightest of the youngest scientists who often do some of their best work of their lives in their early years.

We have included that in our legislation that we passed. You have made a focus of it. So I would like to know, number one, about the progress you are making and what else you intend to do about making sure that a lot of this money is focused on young scientists.

Number two, the peer review panels, some have said to me that the peer review panels are not as high quality as they once were. I do not know if that is true or not. The suggestion was made that anyone who receives an N.I.H. grant, and there are a lot of those, I think you said ten thousand?

DR COLLINS. Eleven thousand.

The CHAIRMAN. Eleven thousand, has to sort of go into the jury pool and be eligible to be selected. They might not all be the very best, but be eligible to be selected for the peer review panel.

The quality of the peer review panels would be my second question.

The third question would be, I have heard some criticism that the proposals have become more conservative, and more bureaucratic, and longer. That at one time, proposals before the peer review panels were shorter, more succinct, and bolder.

What about those three things? What are you doing about them? What is the validity of concern in those areas?

Dr. COLLINS. Well, those are three wonderful questions and I am glad to respond because they resonate with things that we talk about and are doing things about at N.I.H.

With regard to young scientists, totally agree with you that this is critical. This is the future and we have gone from 2003 to 2015 through a tough time for those young scientists where N.I.H.'s purchasing power dropped way back and their likelihood of getting funded got to be to the point where many of them were really quite discouraged.

We have benefited, of course, from congressional enthusiasm for N.I.H. over the last three years and that alone has helped, but we have actually prioritized the young investigators, what we call early stage investigators, to be the ones that we most want to be

sure we are taking care of when they come forward with a new and wonderful idea.

This year, in a program of next generation research initiative, which is actually part of 21st Century Cures, we expect to fund the largest number of early stage investigators ever; 1,100 of them who have never previously gotten a grant.

We also have a very vigorous group, including some graduate students and post doctorates, and junior faculty, who are giving us additional ideas about how we could encourage those early stage folks. They will make a major set of recommendations to me in December, and I think that will add some additional new ideas about programs that we can do.

We want to be sure that people not only see us as a place where they can bring their ideas, but they can bring bold ideas and we want to encourage that as well.

Which is probably coming to your third, and I will come back to the second question, but the third question about conservatism in terms of applications, in terms of the kind of science that we fund. I also worry about that.

We, at N.I.H., have been experimenting quite successfully in programs like the Pioneer Awards, which do not expect a lot of preliminary data, and a quite brief in the nature of the application, but need to propose something that is truly groundbreaking.

With that program now having been in place for almost 10 years, I can tell you that dollar for dollar, it pays off better than our traditional programs and many of the institutes are adopting a similar program. The General Medical Sciences Institute has moved almost all their portfolio into that kind of program, which is a different model and we think is very productive.

Finally, I would say with regard to peer review, we agree that anybody who has a grant from N.I.H. ought to be willing to serve on peer review. We did a survey of that three years ago and discovered there were some exceptions.

As of 2015, it is a condition of your grant award that if you are asked to serve in peer review, you are expected to say yes. And the numbers I looked at over the last couple of weeks, those who are receiving funding from N.I.H., about 80 percent of them are, in fact, now serving in that role.

That includes some younger folks, who maybe the older emeritus folks do not recognize as being sort of the familiar faces they thought they would see on a peer review panel, but we need them to be there too.

The CHAIRMAN. Thanks, Dr. Collins.

Senator Bennet.

Senator BENNET. Thank you.

Dr. Collins, just along the lines of Chairman Alexander's first question, I remember you sitting at, I think, at this very table some years ago talking about the cost of the unpredictability of the funding that N.I.H. was getting at the time, and the difficulty of being able to recruit and sustain academic research if the funding was uncertain.

Can you tell us today with more certain funding what difference that is making on the ground in these research institutions around the country?

Dr. COLLINS. It has made an enormous difference. And again, I think the difficult period from 2003 to 2015 made it hard for investigators to be confident that they could tackle a program that was going to take several years to bear fruit. It made it hard for us at N.I.H., as project managers and as visionaries, trying to design something bold. Could we really be confident that was going to happen?

Let me say that 21st Century Cures was a wonderful antidote to that providing a trajectory for funding for those four signature projects over ten years. We have almost never had that kind of confidence in the future, and that bill made that possible for us to see.

But for the average investigator working in the laboratory to see the way in which this stability has crept into the circumstance, as opposed to the ups and downs, has given them—and I talk to a lot of them every day—the confidence that they are in the right place, doing the right thing, and it is Okay to tackle something that is not going to get solved in a year or two.

I might say the way in which this is happening is such a different landscape now than the world's worst moment for us, which was sequestration, where in March 2013, all of a sudden, we lost \$1.5 billion on one very bad day. That sent ripples through the community that took a long time to recover from, but I think we are getting there.

Now let me say, we are still, I am sorry to say, at the point where if you send a grant to N.I.H. your likelihood of getting funded is only about 20 percent. That is a lot better than the 15 or 16 percent it was, but we are looking forward to being able to see ways to continue to see that rise.

Senator BENNET. Good. I think that is a real testament to Chairman Alexander and Ranking Member Murray's bipartisan support of this Committee at a moment when we are not getting much of that in the U.S. Congress demonstrates that you can actually get some things done.

Dr. COLLINS. We are deeply grateful for that.

Senator BENNET. Well, we are grateful to you.

I sent you a letter with Senator Schatz and asked you a few questions about whether there is a consensus in the scientific community on whether our society is becoming addicted to technology and what the public health effects of social networking are.

Just last week, the American Psychological Association released a study showing that in recent years, 20 percent of U.S. teens reported reading a book, magazine, or newspaper daily for pleasure, while more than 80 percent said they use social media every day.

Additionally, it reported in 2017, it found that children eight years old and older spent 48 minutes a day on mobile devices, up from 15 minutes in 2013. Similarly, 42 percent of children eight years old and younger have their own tablets, a major increase from 7 percent in 2013.

It seems to me clearly we need to prioritize some research here in these areas. Thank you for your response to the letter, but I wonder whether you could talk about what N.I.H. is doing to address these issues?

Dr. COLLINS. Well, I will quickly tell you about a program that is funded by N.I.H, called ABCD, the Adolescent Brain and Cognitive Development Program.

This has enrolled now more than 10,000 nine and ten year olds and is tracking them over the course of ten years to see what influences are happening to brain development, including screen time, including the use of social media, including drug access, and many other things, including brain images that will teach us something about what is happening to the wiring. That is going to be very useful in this regard.

But let me ask, Dr. Bianchi, of the Child Health Institute, because they have recently held an important workshop on this very issue trying to design what the next research steps ought to be.

Dr. BIANCHI. Thank you for your question.

There are really two issues. There are issues on early child development and then there is the issue of technology addiction later on and how it affects adolescents.

NICHD has recently held a workshop in January that has examined some of the neuropsychiatric issues on technology and early brain development. We are particularly concerned about language development, reading comprehension, and also parent-child interactions.

We have come up with a number of recommendations to move forward with that and we are, of course, very interested in your legislation.

Senator BENNET. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thanks, Senator Bennet.

I think the vote has started, so I am going to go vote and Senator Bennet, if you would chair the Committee. I will be back and we can swap the gavel.

Senator Isakson.

Senator ISAKSON. Thank you, Mr. Chairman.

Dr. Collins, welcome. I want to add a comment, if I can, at the beginning rather than a question.

My first engagement with you was at the National Prayer Breakfast when you demonstrated your gifted talent of playing classical music on the guitar, which to this day, was still one of the best performances I ever saw. But I knew then that you were a special person, and then with your success in the human genome, and all that you have done at N.I.H., we are blessed to have you.

But I want to commend you on talking about the National Institutes of Hope. I have Parkinson's, and have had it, been diagnosed for six years. Evelyn, this child has a challenge and her family has a challenge. I am going to tell you about a challenge in our family in just a minute.

But because you are the National Institutes of Hope, there are lots of people who have hope today that did not have it before primarily because you are changing attitudes in this country, both in the institution of medicine, as well as the patients who come in for help.

I want to thank you for having such a positive, solution-based favorable attitude toward research, toward cures, and toward the

process that nothing is impossible if we just work at it. You do a great job and we appreciate it.

Dr. COLLINS. Thank you, Senator.

Senator ISAKSON. As far as Evelyn is concerned, my daughter Julie's best friend is named Julia Vitorello. She is a resident of, was a resident of Washington, DC. She is now a resident of Colorado.

Her baby was born with Batten disease, which is a totally incurable childhood disease which terminates life somewhere around the age of ten or twelve. But it is a degenerative disease like some of the other diseases that have a lot of atrophy involved in them.

She is now at Boston Children's Hospital undergoing a special treatment that has been designed by her doctors who have hope of using gene therapy as a way to transmit and I am out of my league now. I am a real estate salesman. I do not know about the human genome.

But I know this. They are using that gene therapy through the spinal column to get the treatment to the place in the brain it needs to be and they are showing an amazing success. You referred to the gene therapy and some other things.

Would you talk about the gene therapy for just a minute?

Dr. COLLINS. I would love to, Senator. And thank you for your comments. That was most generous.

My colleagues make this job for me the most amazing experience every day because of the talent that you see surrounding me and all the other folks who are not at the table.

Batten disease is one of those incredibly tragic neurological conditions which is caused by genetic misspellings. And so, it is amenable to the idea of gene therapy, but to actually turn that into practice has been decades long and it is very exciting to see this is now starting to work in certain instances.

You saw an example with Evelyn because the disorder that affects her, SMA, affects the spinal cord. For a long time, we thought that would be the hardest place you could possibly imagine getting your gene therapy to be delivered, but you have seen what has happened here; just an amazing experience for all of us to see how this is working.

With Batten disease, likewise, you need to get the delivery into the brain and the spinal cord. Hence, in the protocol you are talking about, the delivery is into the spinal fluid, which then bathes the brain and provides that delivery. I do not know the precise status of that protocol.

I was gratified, though, to see similar circumstances about Huntington's disease. Now, here is one of those incredibly troubling, dominantly inherited conditions. Woody Guthrie, one of my childhood heroes, had Huntington's disease.

In the last few months, again with the gene therapy placed into the spinal fluid, there is clear evidence that they are able to reduce the amount of the toxic protein; an encouraging evidence that it is slowing or stopping the progression of the disease.

Now, that was one of the ones that I thought might be the longest to ever yield up its secrets because of it being affected in the brain this way. But we are starting to see that happen.

None of that happened without many, many years of hard fought progress and a lot of disappointments, but now I think gene therapy is really coming into its own.

Senator ISAKSON. I agree and it is showing great promise, which we hope we will see one day, just like we are seeing in Evelyn right now.

Evelyn, thank you for coming, by the way; my kids always got the shies just like Evelyn does.

One last thing to talk about is what you talked about on the brain. The stimulation in the human brain is now being done to treat Parkinson's and other neurological diseases and making remarkable improvements and remarkable increases. The more we can continue to invest in that, the more we are going to invest in, not cures, but certainly ways to deal with some of the ramifications of neurological disease.

I want to thank all my colleagues on the Committee who helped me working on the Neurological Disease Registry expansion under the 21st Century Cures bill to expand that registry, to expand our information for research.

Thank you very much for being here today.

Dr. COLLINS. We do appreciate that.

Again, the BRAIN Initiative, one of the early results of this is going to be having a better wiring diagram of the brain so the deep brain stimulation, which right now works, but we are not exactly sure why. We will be able to do it much more precisely.

Senator ISAKSON. Thank you very much.

Senator BENNET [presiding]. Thank you, Senator Isakson.

Senator Kaine.

Senator KAINE. Thank you to Dr. Collins and to all. I especially want to thank you, Dr. Collins. You are a great Virginian and you highlighted a wonderful Virginia family when you talked about Evelyn Villarreal. She and her family are from Centreville, I believe. Is that correct? Very, very happy to have you here and to hear the story about the genetic therapy that has made such an advance with respect to children with SMA.

It also highlights the importance of pediatric specific research. I came onto the Committee and I probably had an assumption that research into adult conditions could be just kind of scaled to pediatric conditions. And so often, they are very different.

In 2014, I was proud to support the Gabriella Miller KIDS First Research Act, which increased funding for research on pediatric disease within the N.I.H. by taking a separate, non-health related source of direct funding and putting it into pediatric research. And I think since that bill passed, it has directed about \$55 to \$60 million into pediatric conditions.

There has also been improvements made for promoting such research in the 21st Century Cures Act to include the National Pediatric Research Network and the Global Pediatric Clinical Study Network.

I would love it, Dr. Collins, if you could address this question.

What promise do increasing research and the number of clinical trials in pediatric rare diseases or cancer hold for finding cures for diseases like SMA or like the childhood cancer that killed young Gabriella Miller when she was eleven years old?

Dr. COLLINS. Well, I really appreciate the question. All of us at the table are deeply committed to advancing the cause of pediatric research.

One of us happens to be a pediatrician and that is Dr. Dianna Bianchi. So I will ask her to address some of the points that you have raised, particularly about the Gabriella Miller KIDS First Research Act.

Senator KAINE. Thank you.

Dr. BIANCHI. Thank you for your question. Always appreciate a focus on children.

In fact, the N.I.H. funds \$4.2 billion on pediatric research. Although we have child health in our institute name, research in pediatrics and pediatric conditions is done in virtually all of the institutes and we are all working together to make the best use of that \$4.2 billion.

We fulfilled a mandate of the recent Pediatric Research Network part that was in the Cures Act legislation by having four predominant networks that includes the IDeA States; the Pediatric Clinical Trials Network, which is focused on drugs, testing drugs in children; the Neonatal Research Network; and the Rare Disease Clinical Network, which is looking at over two hundred conditions.

Those four networks are addressing many, if not most, of the conditions.

Now the Gabriella Miller, we have had some successes in that area. I understand you knew Gabriella.

Senator KAINE. I actually did not, but I know her parents very well. They were a great Loudoun County family.

Dr. COLLINS. A wonderful family, I know them also quite well.

Dr. BIANCHI. The Gabriella Miller Network really creates an infrastructure so that researchers can collect large cohorts of biomaterials from children with conditions such as cancer and congenital anomalies.

The infrastructure allows us to work at a very large scale and already has had successes. So we have a childhood cancer dataset that is already publicly available in pediatric Ewing's Sarcoma and we also have datasets that are available for congenital heart disease, cleft palate, and diaphragmatic hernia. Researchers anywhere around the world can make use of that information.

Senator KAINE. Thank you.

Dr. Collins, one other question. You gave me an inspiring answer when you were before this Committee about a year ago—I used the analogy of President Kennedy saying we could be on the moon by the end of the decade, which seemed to many as science fiction, and yet it was doable and we did it—to ask you, could we, as a society make a pledge to be addiction free by 2030 and get there?

You said not only could we, but we knew enough about addiction as long as we appropriately define what addiction free is, we should make such a commitment, and it was not a question about science or understanding. It was just really an issue of will and resources.

I have continued to discuss that as I have traveled around the Commonwealth. Talk to me, if you can—

Actually, I am right near the end of my time. This is probably going to be a long answer. I think what I will do is I will submit

for the record, you did address it in your opening testimony. I would love to know some of the things that you are doing at the N.I.H. to really help us grapple with this problem.

As you know, just last week, the statistics came out; 72,000 Americans died of overdoses in 2017. Hundreds of thousands overdosed; 72,000 died. When I think that is more than the number of Americans that died in the entire Vietnam War, we are losing a war every year to despair and despondency, and your agency has a critical role in helping us figure out how to win that war.

I will ask that question for the record to get status on current projects underway at the N.I.H.

Dr. COLLINS. I would be happy to respond. We are very invested in this.

The Congress gave us \$500 million in the current fiscal year of additional funds to focus on the opioid crisis, and we are deeply engaged in that, and moving very quickly.

Senator KAINE. Great, thank you so much.

Thanks, Mr. Chairman.

Senator BENNET. Thank you, Senator.

Senator Cassidy.

Senator CASSIDY. Hello to you all. I would say gentlemen, but you too, Dr. Bianchi. Thank you all for being here.

You probably know from previous kind of questioning, lines of questions, I have always been concerned about priorities in spending and so, just a couple of things as background.

[Chart 1.]

Senator CASSIDY. The societal cost of disease here and you see that there is roughly, if this is disability life years adjusted and for my colleagues who may not be familiar with this, just an amalgamation. If somebody has an illness, how much do we lose in terms of productivity with an element of death. Then here is just the mortality. This is from 2015. The funding levels are from 2016.

What we see as we look at societal costs of disease, there is roughly a correlation between how much it cost disease, how much it costs society, and the disability and the death rate it causes.

I have two figures for obesity. One is how the CDC just says, "These are the folks who die." And this is everybody for whom obesity is listed on the coroner's report knowing that obesity leads to a lot of other conditions that might be the primary cause of death, for example, heart disease.

Can you hold up the other, please?

[Chart 2.]

Senator CASSIDY. Here you see the N.I.H. funding and we see here is HIV, but obviously a lot for HIV. Here is diabetes. Societal cost. Although we spend a lot on diabetes, it is not as much. I am struck, though.

What I want to emphasize is the obesity. Now, this scale cannot do justice to how much of a difference it costs society in terms of societal costs of obesity relative to funding. So there is the N.I.H. funding by disease where it is \$965 million even though it costs us \$190 billion.

Again, it costs society, obesity, \$190 billion, but we are spending \$965 million. The size of the bubble represents how much money we are spending upon it.

Can you hold up the racial disparity issue?

[Chart 3.]

Senator CASSIDY. As some of you may know, I worked in a public hospital in Louisiana with the uninsured for thirty-five years and you cannot help but notice that there is a racial difference in obesity.

If you look at race, any mention of obesity on a death certificate, African Americans have a much higher rate of obesity. American Indian or Alaskan Native, here is white, here is Asian Pacific. I think if we put Samoans, though, it would bend up like that. So there are some clear racial disparities associated with obesity.

My question, is it just a function of how we appropriate money? Because it does seem that obesity as a primary illnesses is underfunded relative to the societal cost.

Again, \$190 billion societal cost, \$965 million in contrast with some other diseases with far less societal cost, but far more N.I.H. funding, Dr. Collins.

Dr. COLLINS. Well, Senator, it is nice to have another iteration of a conversation we have had over two or three years. I appreciate your perspective on obesity, which I totally agree, is an enormous public health challenge for our Nation.

Senator CASSIDY. By the way, can I just for those who may not know, obesity is implicated in Alzheimer's, implicated in heart disease, implicated in cancer. So although it may not be primary, it is the match that starts the fire for a lot of other diseases.

I am sorry to interrupt.

Dr. COLLINS. No, that is quite all right.

I think your point is taken. The question that we, at N.I.H., are always wrestling with—and you have seen the way we have played this out in our strategic plan that we put forward a couple of years ago that tried to really articulate how we set priorities—is this balance between public health need and scientific opportunity.

I think with obesity, we would all agree that the problem is a multi-factorial one. That there are many aspects of this that relate to things that N.I.H. probably cannot control in terms of diet, lifestyle, even the built environment, and so on. We are studying those things pretty intensively.

In terms of interventions, though, to do something about this epidemic, which is a fairly recent one, it does not look as if a medical therapy is on the edge of happening. And so, it is a bit of a different circumstance than, say, HIV/AIDS where we have a vaccine.

Senator CASSIDY. If I may interrupt, Dr. Collins, in all due respect. In the past, you have told me, and I will not mention the institutes, but you have said, "Well, we do not really fund that because we are really not on the cusp of great advances."

I go speak to the director of the same, without mentioning your name, and he says, "You have got to be kidding. We have so much opportunity here." That was kind of repeated several times.

If I spoke to obesity researchers, they may start speaking about microbiomes, and leptin, and all this other stuff that again, kind of quickly passes my level of knowledge.

But it does seem to be self-filling that if you say, "We are not going to fund it because we are not ready to go to primetime in our

research,” you never go to primetime in your research because you never have the requisite prefunding.

Dr. COLLINS. I think we are ready to go to primetime in research with obesity. It is a question of where are the scientific opportunities.

You mentioned the microbiome. That is certainly a very powerful one. Clearly, learning things there plays out both in terms of obesity and diabetes, for which a big investment is being made.

Although, some of that research might not actually score as obesity; it might score as it is a diabetes project or it is a nutrition project. Some of this, therefore, is just the bookkeeping part. But I take your point.

Again, I think this is something we worry about every day when we meet as institute directors around the table on Thursday morning. Are we setting our priorities properly?

Your input has been very helpful in that regard.

Senator CASSIDY. I would just suggest that we begin to focus more upon obesity, which seems to be an outlier in terms of lack of funding relative to societal cost.

I now defer to whichever of my colleagues on the other side of the aisle is due.

Senator COLLINS [presiding]. Senator Warren.

Senator WARREN. Thank you.

The National Institutes of Health funds this country's top researchers and doctors. N.I.H. grants fuel medical breakthroughs, help universities pursue cutting edge science. I want to talk about money, because I understand N.I.H. needs money to be able to do its work.

The vast majority of the N.I.H.'s funding comes from taxpayers. But in 1990, Congress established the Foundation for the National Institutes of Health, a nonprofit foundation that solicits private donations to support N.I.H. research. That means that if a drug company, or a device company, or a big tech company, or a lobbying firm wants to fund N.I.H. research, they can do so by donating to the N.I.H. Foundation.

Dr. Collins, according to the most recent list of donors, the top six largest contributors to the Foundation for the N.I.H. are all drug companies. Each of these drug companies has donated to the Foundation every year for at least the past fifteen years. Let me just ask this question.

Do you agree that science should be setting the agenda at N.I.H., and not donors?

Dr. COLLINS. Absolutely.

Senator WARREN. Good.

I understand that is how it is supposed to work. The N.I.H. comes up with a plan based on science and the Foundation gets donations to fund it, but when you have your hand out for cash, it is sometimes possible that these lines get blurred.

The N.I.H. recently canceled a study of the health effects of alcohol consumption following an internal investigation that revealed that the alcohol industry was not only funding the study, but that the study had been set up to deliver the results the industry wanted.

This is not even the only case this year that has raised ethical questions.

In April, you pulled the plug on a plan to take hundreds of millions of dollars from drug companies that make opioids, some of which are under investigation for causing the opioid crisis in the first place, and using that money to fund a study to treat addiction.

Let me ask this question, Dr. Collins. If these donations from industry are raising so many ethical questions, why should N.I.H. accept them at all?

Dr. COLLINS. Well, we are thinking a lot about this in the wake of the examples that you have just cited. But as N.I.H. director of the last nine years, I can also cite you some examples where this kind of partnership with industry has actually made science move faster than it otherwise would have.

Take the Accelerating Medicines Partnership, a project which involves ten pharmaceutical companies working on diabetes, on Alzheimer's disease, on rheumatoid arthritis, and very recently adding Parkinson's disease to that.

In those instances, this was all precompetitive research. The data was immediately accessible. It brings around the same table scientists from both public and private sectors who design together what the research ought to be, building on the strengths of both groups. And it advances the cause of science more rapidly than might otherwise happen.

There are no strings attached to the money that is provided by the drug companies, basically, that goes to the Foundation for N.I.H. It is used to support this program that is totally public about what we are doing. I would defend that. It has been a very good thing.

What we need to be careful about, and which has, I think, caused us to stub our toe here a couple of times, is a circumstance where the source of the funds has a vested interest in a particular outcome of the study.

We have started a recent study on cancer immunotherapy that Dr. Sharpless is leading. Again, involving industry input, trying to identify what are the biomarkers that indicate whether immunotherapy is going to work. Everybody wants to know the answer to that. Nobody has a stake in what the answer is going to be. Only that we need the answer. This is a really good example of how to work together.

We just have to be thoughtful about exactly what the design looks like.

Senator WARREN. I appreciate that and I am really glad you are working to address the ethical landmines in this area.

I think the N.I.H. should be getting more funding, but I will be blunt. If drug companies and rich donors want to chip-in for more N.I.H. research, they should do it through their taxes like everyone else. I would be happy to write the bill to bump up their contributions.

But here is the bigger issue. Forcing an agency to beg for contributions for money just to carry out its essential mission is a glossy invitation for corruption.

I believe it is time to end the influence of corporate money in Washington, and that means calling it out and shutting it down in whatever form it takes.

Thank you very much. I appreciate the work all of you are doing.
Senator COLLINS. Thank you.

As luck would have it, I now not only get to be Chairman for a brief time, but I am up next for questions.

[Laughter.]

Senator COLLINS. Dr. Collins, it is always great to see you. I continue to claim you as my cousin and I hope you will not disabuse others.

Dr. COLLINS. I am honored to be claimed.

Senator COLLINS. The 21st Century Cures Act provided multiyear funding for the Regenerative Medicine Innovation Project.

At MDI Biological Laboratory in Maine, researchers are working with a team from Jackson Labs in Maine and the Maine Medical Center Research Institute in an N.I.H.-led effort on kidney regeneration—Dr. Hodes may want to comment on this also—to address the high health care costs associated with treating chronic kidney disease.

I visited the Maine Medical Center Research Institute, and it is absolutely fascinating the work that is going on.

Could you tell us whether you are seeing any results yet from the Regenerative Medicine Initiative? I know it is early.

Dr. COLLINS. I would love to talk about that and appreciate that this was included in 21st Century Cures as one of the four initiatives with specific call outs for extra funding.

Certainly, this idea of being able to build whole organs from stem cells is one of the things that has really electrified a lot of the community. You could call this tissue engineering. What is happening with hearts and with kidneys is particularly of interest.

If I had thought to put it in my briefcase today, I could have brought you a little kidney on a chip that has actually been synthesized by a different group, but very much working with the folks in Maine as well, because this is a very integrated community.

The idea that we could figure out the appropriate kind of signals to send a stem cell that might have been derived from your skin and convince it that it should become your next kidney seems like science fiction, but maybe not so much.

So far, these are pretty small renditions, but I have seen some of these that actually have a bit of a blood circulation. And even, if you will pardon me, can make a little bit of urine. So we are on the path here.

Ultimately, what we hope is this could become an alternative to the need for a transplant for somebody whose kidneys have failed. And, of course, along the way, we learn a lot about normal kidney biology that maybe can keep peoples' kidneys from failing because we will have better signals about how to prevent that.

Your group in Maine is a very important one in this effort. I am glad you have been by to see them.

Senator COLLINS. It truly is miraculous work that they are doing and it is so exciting to me.

As you are well aware, Dr. Collins, I have been the Founder and co-chair of the Senate Diabetes Caucus and the Alzheimer's Disease Task Force for many, many years.

Dr. COLLINS. Yes.

Senator COLLINS. As our population is growing older, we are seeing an increase of incidents in both those diseases.

There is also some intriguing science that suggests that there may in some cases be a link between the two diseases as well as cardiovascular disease.

Could you tell us what kinds of findings you are seeing in that area and what promising research is underway?

Dr. COLLINS. That is a great question. I am going to ask Dr. Hodes—

Senator COLLINS. That would be great.

Dr. COLLINS.—Our international expert on Alzheimer's who also knows a lot about diabetes to respond.

Senator COLLINS. Thank you.

Dr. HODES. Thank you for that question, Senator Collins.

There has been extensive collaboration with investigators interested in diabetes and those in neurodegenerative diseases such as Alzheimer's and related dementias. It has taken several forms and areas.

It has been known for some time, for example, that diabetes is a risk factor for Alzheimer's disease. There have been metabolic parallels and similarities between diabetes and what goes on in the brain. In fact, some have called Alzheimer's disease a Type 3 diabetes because of an inadequate effect of insulin.

It is perhaps most graphically translated now into a clinical trial that is ongoing using an intranasal route for introducing insulin to the brain to look for its impact on progression of Alzheimer's and cognitive decline.

At the basic science level and now translated into real clinical trials, very much aware of the commonalities and ways in which we have to borrow and form across disciplines and across silos in order to best accomplish our goals.

Senator COLLINS. Thank you very much.

Senator HASSAN.

Senator HASSAN. Well, thank you very much, Madam Chairman.

Good morning to this extraordinarily distinguished panel. Thank you all for being here and thank you for the work you do.

As you know, Dr. Collins, the fentanyl, heroine, and opioid epidemic is ravaging my State of New Hampshire and communities across our country. I was very proud to work with the rest of the New Hampshire delegation to secure a truly significant increase in funds for the Granite State to use for prevention, treatment, and recovery through the Substance Abuse and Mental Health Services Administration's State Opioid Response Grants.

Now, New Hampshire is receiving \$23 million for Fiscal Year 2018; before that, it was \$3 million. So we think there is potential to really have an impact on the ground.

I think it is really important that we stay focused on making sure that the hardest hit states, the states with the highest mortality rates, get the concentration of funds they need.

But we also need to make sure that we are supporting science here because we need more and better ways to treat addiction and also to manage pain. It is a critical part of curbing the opioid crisis and I appreciate the conversations we have had about it.

I also appreciate very much the work the N.I.H. is doing on the HEAL Initiative to advance this science. When you were before this Committee last, you explained that you needed more flexibility from Congress to allow the N.I.H. to fund research on the opioid epidemic more quickly and efficiently.

Since that time, I have been really pleased to work with Chairman Alexander, with Ranking Member Murray, and Senator Young to introduce the Advancing Cutting Edge, ACE, Research Act to give the N.I.H. the flexibility it needs to quickly advance research on new treatments and non-addictive painkillers by providing them other transaction authority that we have talked about.

Dr. Collins, how will the other transaction authority provided by the ACE Research Act help the N.I.H.'s work on the opioid epidemic including through the HEAL Initiative?

Dr. COLLINS. Well, I appreciate the question and your support of this other transaction authority. Let me explain why it would be so useful and why the timing is really kind of urgent right now.

Of the HEAL Initiative that you mentioned, HEAL standing for Help End Addiction Long-term. One of the projects that we are most excited about, which is truly ambitious, is to see if we could identify maybe three places in the Nation where a particularly hard hit circumstance is happening with opioids.

Then bring together in a way that has not happened before, but as a research enterprise, all of the players in that—the primary care doctors, the emergency rooms, the police, the fire departments, the criminal justice system, all of the other support systems, the state health departments—and see what could we actually do if everybody worked together in a coordinated way to tackle this problem? No single one of those is going to be able to be successful in ending this terrible national crisis.

To be able to do that, which has never really been attempted before, having the kind of flexibility where we could actually reach out and identify partners who maybe have never written an N.I.H. grant and say, "We want you."

Senator HASSAN. Right.

Dr. COLLINS. Also have a very active role at N.I.H. managing this effort in a fashion which, with grants, sometimes we cannot do.

It would allow us to go faster and more effectively. We are going to try to do this anyway, but if we had other transaction authority, maybe in the next month, it would make a big difference in our ability to carry out that part of the HEAL Initiative.

Senator HASSAN. Well, I thank you for that. I am glad to see the bill passed the House and I hope the Senate will act soon on this—

Dr. COLLINS. I do too.

Senator HASSAN. —Along with the entire opioid package that we passed out of this Committee.

I want to go to one other New Hampshire issue, if I may, but again one that has applications all across the country.

Families in my state continue to have questions about what PFAS contamination in drinking water means for their health and the health of their children. Once used for a variety of commercial and industrial applications, PFAS have seeped into water tables in many places, including New Hampshire.

There is a critical need to better understand and address any potential adverse health effects the contaminants may have on our communities.

Dr. Collins, what is the N.I.H. doing to study these chemical compounds and their potential health effects on Americans?

Dr. COLLINS. Well, this is a significant environmental concern and I know in New Hampshire, there has been even a public discussion about it in Exeter that the E.P.A. came and led. Michigan is very much also caught up in this, particularly around Kalamazoo.

Senator HASSAN. Right.

Dr. COLLINS. This is the kind of a substance that has a very long half-life. It is not naturally occurring, but has found its way into many groundwater and water supplies because of manufacturing of things such as carpet cleaners and so on.

In terms of the environmental risks, we really do not know enough about the human risks to be very confident in saying whether this is really a big deal or whether actually we humans are able to handle it. We do know in animals, there is an association with immune consequences and maybe other things including, perhaps, cancer. But the human data is very uncertain.

There is a big project which D.O.D. is funding which our NIEHS, National Institute of Environmental Health Sciences, is part of along with the C.D.C.'s ATSDR. That is going to, I think, provide the kind of data that we currently do not have, at least in terms of the epidemiology of what is the relationship of exposure and to human medical problems.

We desperately need more information of that sort.

Senator HASSAN. I thank you and I agree with that. And I thank you for allowing me to go over, Madam Chairman.

I am going to follow-up just to pinpoint any other gaps in research that you all might see, and I appreciate very much, again, all your work.

Dr. COLLINS. Be glad to do it.

Senator COLLINS. Thank you.

Senator Smith.

Senator SMITH. Thank you, Madam Chairman.

Thank you very much all of you for being here today. It is a very interesting panel. Though as is often the case, we are kind of coming and going from votes.

If I have a moment, I would like to follow-up on the questions that Senator Hassan started. But I would like to start, actually, with something different.

I want to start out by saying I really believe in the power of innovation in biomedical research. Coming from my home State of Minnesota, which is such a center of excellence both at the University of Minnesota and also Mayo Clinic.

Senator Collins was talking about the power of regenerative medicine, which is also something that we have been working on

intensely in Minnesota, especially through Mayo Clinic. So I believe very strongly in that.

But I also believe that if people cannot afford the therapies and the medicines that we are imagining, that we are creating, then we have a real problem. I have to tell you that this is the No. 1 issue that I hear about from Minnesotans, whether it is figuring out how to pay for a therapy like insulin, which has been around for 100 years, to figuring out how to pay for the most recent cancer breakthrough medicines. It is a huge problem.

A lot of these therapies, of course, have been created because of help from the National Institutes of Health. I am told that every one of the 210 new drugs approved by the FDA between 2010 and 2016, N.I.H. contributed to.

What happens, of course, the cost of innovation is often the reason why medicines cost so much. Yet, in some ways, I think, taxpayers feel like they are paying twice. Once for the support to N.I.H. and then once again when they are asked to pay for these exorbitantly priced medicines when they show up at the pharmacy.

Tell me a little bit about how you see the role of N.I.H. in helping to make sure that we do not only have innovation, but we also have innovation that people can afford.

Dr. COLLINS. Obviously, this is a source of much discussion and much concern. I think you are echoing a lot of the views of the public about how this drug pricing issue is going to be wrestled to the ground and make it possible for people who need access to obtain that.

We, at N.I.H., as you quoted this recent study, just published in the "Proceedings of the National Academy of Sciences of the United States of America," where Fred Ledley and colleagues looked across a five-year or a six-year period and said every single one of the FDA-approved drugs in that timetable were based upon basic science discoveries that N.I.H. has supported.

Some of those were basically to discover, "Here is a drug target," and then a company went and made the drug that hit that target. So it is not as if we basically started making pills and somebody else—

Senator SMITH. There is a difference between commercialization and basic research, which I understand.

Dr. COLLINS. I think you could say that the system in the United States, this ecosystem between basic science, much of it supported by N.I.H., and commercial application has been the reason that we have been so successful in making medical progress.

But the prices are certainly a concern.

We do not have a lot of levers to pull in terms of direct influence on how a price is set for a newly innovated kind of therapeutic. What we do, and what we can do more of now because science is going forward, is to make it possible for the successes to happen more often.

One of the reasons drugs are so expensive is that the failure rate for a company trying to get something across the finish line is about 99 percent. And so, when you finally get something that works, you have all of that other stuff that you have spent money on that got you nothing; that has to be somehow accounted for.

At the National Center for Advancing Translational Sciences, which is part of N.I.H., we are identifying the areas that lead to that high failure rate systematically in coming up with new technologies to make that less likely to happen.

If the success rate was just 5 percent instead of 1 percent, it would make a huge difference in the overall financial circumstances that companies face. We are pushing as hard as we can on that. That is probably our best contribution.

Senator SMITH. Well, I think that is an important issue for us all to work on together. It is basic access to these incredible therapies that are being created is fundamental to whether our health care system works at all.

For those of us who watch this and try to understand it, and we understand what you are saying, but we also see that these big companies are making a ton of money, and yet, we are all paying. That is, I think, the fundamental issue that I am grappling with and trying to find solutions to.

I would like to be able to—because innovation is so important and affordable drugs are so important—I would like to be able to work together on that.

Mr. Chairman, I am out of time, but I would like to submit to the record and for follow-up a question having to do with what Senator Hassan was talking about.

In Minnesota, we call it “diseases of despair”. The significant uptick, 40 percent increase in suicide, and other diseases related to behavioral health, and opioids, and addiction. What we can do and how we can work with N.I.H. on that.

Dr. COLLINS. Glad to.

Senator SMITH. Thank you.

The CHAIRMAN [presiding]. Thank you, Senator Smith.

Senator Jones.

Senator JONES. Thank you, Mr. Chairman.

Thank you, Dr. Collins, and the whole team for being here and for the incredible work you do that touches on every family in America. I really appreciate that.

A couple of weeks ago, I had the privilege of meeting with some of the leaders at the University of Alabama in Birmingham, which I consider to also be one of the leading institutions of not only higher learning, but research in the country.

Specifically not only have I met with them with a comprehensive cancer institute, and all the work that they are doing there, but I had a chance to talk about their precision medicine program.

I know that everyone is excited about the All of Us Research Program because precision medicine truly has potential to be a game changer for delivering the right treatment to the right person at the right time. I am so happy that Alabama is playing a role.

Dr. Collins, just a very general question, what is it Congress can do other than just continuing to try to fund at the levels—and I also commend Chairman Alexander and Ranking Member Murray about the work on this—is there something else specifically that we, as Members of Congress, can do to really help promote and accelerate the use of precision medicine in this country?

Dr. COLLINS. I appreciate you raising this issue and mentioning the All of Us programs.

In response to your “what could we do?” maybe it would be useful, in fact, for Congress to become an ally with N.I.H. in encouraging people to take part in this unprecedented national experiment where we are asking 1 million people to sign up. I think we mentioned, we just hit 100,000 today. So we have a little ways to go, but it is a really wonderful start. I appreciate the way in which UAB is a critical part of this partnership in the south.

We can have people sign up either by direct volunteer, where they basically get online, JoinAllOfUs.org and sign up. Or, if they are nearby to one of the health provider organizations that is a partner with us and get their care there, they can sign up in that fashion.

We are hoping to see this really go forward quite quickly. And any kind of assistance we could have in terms of local events to raise the enthusiasm for this.

This is taking what we have learned from a program like Framingham, which taught us an awful lot about cardiovascular disease, and extrapolating it by about a factor of 40 in terms of the size, in covering all diseases, not just cardiovascular. Everybody sitting at the table has a stake in all of us turning out. We will enroll children starting next year as well.

Senator JONES. I appreciate that and I will tell you, even before you said that, one of the things that I discussed with them at UAB was that at some point in the very near future that my wife and I will go, and we will sign up, and we will try to make an event of that. I will encourage all of my colleagues to do the same.

Let me move on to one other question that I had and you touched on this earlier in your testimony in response to a question. That is about developing the next generation of talented biomedical researchers, which is an extraordinary effort, and I applaud that effort.

But one of the things that I am concerned about is trying to reach into underserved communities. It seems that we are missing such talent that is out there whether they are researchers, or whether they are doctors, or lawyers.

What can we do as part of the programs that we have got now to specifically reach into underserved areas to try to grab that talent out and give them that extra boost that they need? Because they do not always have the same chances as some of the kids in the more urban areas and schools that have a lot more money.

Dr. COLLINS. Well, I really appreciate that point because this is an area of great interest and concern.

N.I.H. has been working for decades in trying to increase the participation in our research workforce by people from all different backgrounds. And frankly, we have not been that successful in many of those decades in terms of making this happen. Our workforce is still underrepresented when it comes to African Americans, and Latinos, and Native Americans.

But we have a couple of new programs that are now underway for about three or four years that are starting to show promise. One of them is to recognize that a lot of that talent does not necessarily end up in a research intensive four year college environment, but has the interest in getting involved in research.

The thing that really makes that interest turn into a reality is the chance to take part in a real research project. Not hearing about it in a lecture hall, but actually doing research yourself.

The program called BUILD, which we have started three years ago, is a partnership between universities that have a lot of under-represented groups in their student body, but do not have the research opportunities that would really benefit. They partner up, with some funds from us, with institutions that do have those research capabilities to give those talented folks a chance to see what that is like.

The other thing that is often missing is mentoring. If you do not see anybody who looks like you who is a role model, it is a lot harder when you hit a bump to imagine that this is your future.

We set up a whole National Research Mentoring Network to connect people up. If you do not have somebody down the hall from you, well, maybe there is somebody in your town, or even in your state, or even just somebody you can talk to on the phone who has lived the life that you are trying to live. That seems to be a big encouragement too.

We are evaluating this at every step along the way. I know this is a hard problem. I am not going to declare victory yet, but I am seeing real progress.

Senator JONES. Well, thank you very much and thank you for your efforts. Thanks to all the Committee. I see my time is up, Mr. Chairman. I will probably have a couple of questions particularly about infant mortality and maternal mortality, which I think is something that is going underreported today.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Jones.

Senator Bennet.

Senator BENNET. Thank you, Mr. Chairman. I just had a couple of remaining questions.

Dr. Collins, after we passed 21st Century Cures, we worked on and were able to pass, thanks to the Chairman and the Ranking Member, the RACE for Children Act as part of the FDA User Fee package. I know that NCI has been collaborating with the FDA on the implementation.

As you know, the bill directs pharmaceutical companies to study some of the most innovative cancer drugs for children when treatments are effective for adults and that may be a benefit for children. Some of the treatments maybe immunotherapies that use the body's own immune system to fight cancer. I understand that some of these therapies have been successful in treating certain pediatric cancers, yet other approaches have not been as effective.

I wonder whether you could talk a little bit, Dr. Sharpless actually, about what NCI is doing to ensure children will benefit from promising advances in cancer immunotherapy.

Dr. SHARPLESS. Thank you. This is an exciting area.

As you alluded, there is a lot of progress going on in cancer research. A lot of new therapies have become available; a lot of excitement, a lot of new targets.

But because of the structure of the commercialization of novel therapies, there is sometimes a disincentive, actually, to test these therapies in children.

I think the RACE Act was laudably intended to encourage pharmaceutical companies to develop their drugs for pediatric use, in addition to adult use, when the target was relevant in children. I think it is a smart way to do it.

I think it is not onerous on the drug companies. It does not hurt innovation, but it still provides a real emphasis on childhood cancer, which is an area where we had seen a lot of progress, but we still need a lot more.

The RACE Act directed the NCI and the FDA to work together to develop a list of these relevant targets and that list is now developed through a series of meetings between the NCI and the FDA. It has been published online and it is seven pages of molecular targets that, if you are making a drug to this target, you have to have a plan to test it in children.

Now, we eagerly await to see how this is implemented. We have every expectation the pharmaceutical companies will comply with this law and will really change their practices.

Senator BENNET. Well, that is good to hear. Thank you very much.

Finally, Dr. Collins, appreciate the update you provided on the Precision Medicine Initiative, particularly with respect to the All of Us Research campaign you were talking about. Saying it is going to give researchers a lot more data to predict prevention and treatment needs.

As we begin to think about the future of precision medicine, I just wanted to know whether you think N.I.H. needs additional authorities to keep up with the fast pace of science.

Researchers in Colorado have been at the forefront of some of these biomedical advances. There are more than 720 biomedical companies in my state employing almost 160,000 Coloradans through direct and indirect jobs, many of which, almost all of which actually pay extremely well.

When we think about the hope of personalized medicine and the level of innovation we are seeing, what is the best way for us to follow-up on 21st Century Cures as we think about it?

Dr. COLLINS. Again, I think what the 21st Century Cures bill provided over a very thoughtful two years of selecting and hearing from various stakeholders about what would be most useful did, in fact, incorporate from our perspective, a number of legislative authorities that we greatly value.

There was a question from Senator Hassan about this other transaction authority being granted, our ability to use that in the common fund and to use it in the All of Us Precision Medicine Initiative has made a lot of difference in the ability to move quickly.

We would actually be grateful to have an even broader authority for other transaction authority in other places. The Chairman and I have talked about that. As we have gotten more experience with it, it is perhaps more rapid moving. Maybe people worry it is a little bit riskier because it can be rapid moving, but in certain instances, has made all the difference. So that would be an area.

Another area if we had the opportunity to expand our authorities, when we get to a place where we really have an opportunity to do an assessment of a precision medicine strategy, it is not interesting to the private sector. The ability to carryout Phase 3 trials

within the National Center for Advancing Translational Sciences would be of value. At the present time, that is not something we have the authority to do. That is just another example of something that could help us.

But again, I cannot say enough about the way in which 21st Century Cures basically took our list of things that we hoped to be able to do and pretty much checked the boxes one by one, and has made it so much more possible for us to move quickly.

Senator BENNET. Thank you, and thanks to everybody.

I actually cannot leave. I cannot resist asking Dr. Fauci, before we go, what are you worrying about these days?

Dr. FAUCI. Thank you for that question, Senator.

As you probably would have guessed, I always worry about the emergence of an infectious disease such as we usually use the prototype of pandemic influenza, a respiratory illness that spreads rapidly and that has a high degree of morbidity and mortality.

It is for that reason that I have been, and my colleagues and I have been, working on that for the last at least a decade, but more intensively over the last couple of years, on the development of a universal influenza vaccine that would not only be important to obviate the need to get a vaccine every single season and try to guess, hopefully correctly, what the next season's flu is going to be.

But also to be able to immunize children at a very early age like we do with measles, mumps, and rubella to protect them from the possibility of an unexpected catastrophic outbreak like we saw in the pandemics that we have experienced.

As a matter of fact, we have just very recently had a major meeting of individuals from throughout the country and world to help us formulate a strategic plan to develop a research agenda for the development of universal flu. You have asked Dr. Collins and I, many people do, when is this going to happen?

We now have phases of Phase 2 and Phase 3 clinical trials that look very promising. And just literally in the next day or so, there is going to be an announcement from the University of Pennsylvania of a very, very interesting approach toward vaccines that involves recombinant DNA technologies that are really going to be very important.

I have here just for your staff if you want it, a paper that we just recently published in the "Journal of Infectious Diseases," which outlines our strategic plan for the universal influenza vaccine and our research agenda.

That is what I worry about, but we are trying to do something about, but we are trying to do something about what I worry about.

Senator BENNET. Thank you, Mr. Chairman.

The CHAIRMAN. Thanks, Senator Bennet.

Thank you, Dr. Collins, and to each of you for your extraordinary service to our country. Dr. Fauci, that was one of Dr. Collins's bold predictions about the universal vaccine and it is good to hear that it is on the way.

We are glad to see a significant new and consistent source of funding directed toward the National Institutes of Health. But we want to make sure that we spend every single dollar as wisely and effectively as possible.

We hope this hearing and other tools that we give you, either through 21st Century Cures or the authority to use money in different ways, if you will let us know what you need. Senator Bennet has been a leader in many of these bills. A lot of bipartisan support for breakthrough initiatives and we want to create an environment where you can succeed.

The hearing record will remain open for 10 days. Members may submit additional information for the record within that time, if they would like.

The HELP Committee will meet again on Wednesday, August 29 when we will hear from Dr. Scott Gottlieb, Commissioner of the Food and Drug Administration.

Thank you for being here.

The Committee will stand adjourned.

QUESTIONS AND ANSWERS

RESPONSE BY FRANCIS COLLINS TO QUESTIONS FROM SENATOR
ALEXANDER, SENATOR ROBERTS, SENATOR YOUNG, SENATOR ENZI,
SENATOR COLLINS, SENATOR BURR, SENATOR MURRAY, SENATOR
CASEY, SENATOR BALDWIN, SENATOR WARREN, SENATOR KAINE,
SENATOR SMITH AND SENATOR JONES

U.S. SENATE
 COMMITTEE ON HEALTH, EDUCATION, LABOR AND PENSIONS
 “PRIORITIZING CURES: SCIENCE AND STEWARDSHIP AT
 THE NATIONAL INSTITUTES OF HEALTH”

AUGUST 23, 2018
 QUESTIONS FOR THE RECORD
 NIH DIRECTOR FRANCIS COLLINS

Senator Alexander

- **The NIH-wide Strategic Plan was published in 2015 for Fiscal Years 2016-2020. The 21st Century Cures law requires an NIH-wide strategic plan to outline the direction of biomedical research investments made by NIH, facilitate collaboration among the research institutes and centers and advance biomedicine. That plan is intended to inform the individual strategic plans that each institute or center is also required to have.**
 - **How has the strategic plan been used to guide prioritization of research and encourage wise use of taxpayer dollars at NIH?**
 - **How are the individual institutes and centers incorporating the objectives and priorities established by the NIH-wide strategic plan into their own plans?**

Answer:

In December 2015, NIH released the NIH-Wide Strategic Plan, Fiscal Years 2016-2020: *Turning Discovery Into Health*.¹ The Strategic Plan outlines a vision for biomedical research to capitalize on new opportunities for scientific exploration and address new challenges for human health and has been used to guide priority setting across NIH. The plan focuses on four essential, interdependent objectives that guide NIH’s priority setting over the five-year period that it covers.² These are to: advance opportunities in biomedical research; foster innovation by setting NIH priorities; enhance scientific stewardship; and excel as a federal science agency by managing for results. As stated in the Strategic Plan, NIH will continue to strengthen its commitment to a transparent, evidence-based process of funding prioritization. NIH relies on a multifaceted approach for priority-setting and funding decisions that involves taking into account scientific merit and opportunities, public health needs, and portfolio balance.

The NIH Strategic Plan has been used to guide prioritization of research and encourage wise use of taxpayer dollars at NIH, including improvements and enhancements to NIH’s priority setting process itself. For example, the Plan catalyzed the development of new and enhanced approaches to encourage innovation and ensure support for research in high priority areas. This includes the use of more nimble funding mechanisms such as Prize authority to engage the public in developing novel and innovative solutions to biomedical problems. The *Follow That Cell Challenge*—to stimulate the development of new tools and methods to predict the behavior and function of a single cell in a complex tissue over time—and the *Antimicrobial Resistance*

¹ <https://www.nih.gov/about-nih/nih-wide-strategic-plan>.

² <https://www.nih.gov/news-events/news-releases/nih-unveils-fy2016-2020-strategic-plan>.

Diagnostic Challenge—to develop rapid point-of-care laboratory diagnostic tests to combat the development and spread of drug resistant bacteria—are two such examples. The Plan has also spurred the development of trans-NIH plans such as the new Strategic Plan for Data Science,³ which provides a roadmap for modernizing the NIH-funded biomedical data science ecosystem.

The 21st Century Cures Act requires that strategic plans of individual NIH Institutes and Centers (ICs) be informed by the NIH Strategic Plan and are developed using a common template. The NIH Strategic Plan is not intended to prescribe the scientific priorities of each IC; they will continue to identify the scientific goals that fulfill their individual missions and develop their portfolios accordingly. However, following the release of the NIH Strategic Plan, ICs are now working to harmonize their individual strategic plans with the NIH-wide Strategic Plan so that the format of the IC strategic plans are aligned with the NIH-wide Strategic Plan. ICs will make these alignments when they next update their individual plans. ICs have also been asked to adopt the guidelines set under the Foster Innovation by Setting NIH Priorities and Enhance Scientific Stewardship sections of the NIH-wide Plan. The NIH-wide Strategic Plan will not lead to changes in IC budgets, as these are set by Congress.

ICs and trans-NIH program offices within the NIH Office of the Director (OD) are applying the strategies of the NIH-Wide Strategic Plan towards updating their own strategic plans and have taken the opportunity to clearly delineate their priority setting approaches. For example, the NIH Office of Disease Prevention (ODP) just released a new strategic plan for 2019-2023, with its four overarching objectives aligned to those of the NIH Strategic Plan, and referring strategies back to those of the NIH Strategic Plan throughout.⁴ As an illustration of this, in the second objective, focused on the process of setting priorities, ODP outlines how it will work with federal partners to strengthen the collection and integration of disease burden data into its priority-setting process, as set out in the NIH Strategic Plan.

Other examples include:

- The National Institute of Nursing Research 2016 Strategic Plan reaffirms its commitment to promote research that reduces the burden of disease on patients and caregivers.⁵
- The National Institute on Alcohol Abuse and Alcoholism Strategic Plan 2017-2021 builds on recent advances to address the many public health challenges caused by alcohol misuse.⁶
- The National Library of Medicine 2017-2027 Strategic Plan emphasizes commitment to building a data infrastructure that will support the future of biomedical research.⁷
- The National Institute of Environmental Health Sciences 2018–2023 Strategic Plan outlines goals for enhancing environmental health sciences through stewardship and support.⁸

³ https://datascience.nih.gov/sites/default/files/NIH_Strategic_Plan_for_Data_Science_Final_508.pdf.

⁴ <https://prevention.nih.gov/about-odp/strategic-plan-2019-2023>.

⁵ https://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/NINR_StratPlan2016_reduced.pdf.

⁶ https://www.niaaa.nih.gov/sites/default/files/StrategicPlan_NIAAA_optimized_2017-2020.pdf.

⁷ https://www.nlm.nih.gov/pubs/plan/lrp17/NLM_StrategicReport2017_2027.pdf.

⁸ https://www.niehs.nih.gov/about/strategicplan/strategicplan20182023_508.pdf.

- **What criteria does the National Library of Medicine use to select journals that are already indexed in the MEDLINE database for review and potential removal? Please detail any criteria considered when selecting journals for review and the scoring methodology the Literature Selection Technical Review Committee uses in conducting such review, including whether any criteria are weighted and how the Committee ensures consistency in scoring.**
- **According to the NLM website, journals may be deselected “for various reasons including, but not limited to, extremely late publication patterns, major changes in the scientific quality or editorial process, and changes in ownership or publishers.” Please describe the other reasons not specifically listed above for which a journal may be deselected.**
 - **Are journals provided with a justification for removal?**
 - **Is there an appeals process for journals removed from MEDLINE?**

Answer:

The Literature Selection Technical Review Committee (LSTRC) is a Federal Advisory Committee comprised of 15 members, who are outside experts in medicine, biomedical research, scholarly communication, medical librarianship, and related disciplines, plus consultants for domain-specific expertise as needed. LSTRC is chartered to recommend journals for inclusion in MEDLINE following an established set of elements. LSTRC membership and general processes are described on the NLM website.⁹

The committee recommends an overall score based on their expert review of the journal. NLM leadership receives the LSTRC’s recommendation and decides whether to index a journal in MEDLINE. Elements LSTRC considers when reviewing journals for indexing in MEDLINE include:

- scope and coverage (e.g., content predominantly on core biomedical subjects);
- scientific merit of journal content (i.e., validity, importance, originality, contribution to coverage of the field);
- quality of editorial work to ensure objectivity, credibility and quality of its content (e.g., procedures for selecting articles, peer review, issuing corrections and retractions, handling conflicts of interest, following best practices for protection of research participants);
- production quality;
- journal audience; and
- type of content (original research, reviews, case reports, data articles)

The LSTRC final score and recommendation are based on the overall appraisal of a journal’s scientific content, quality, importance, editorial policies, and subject coverage, and are not based on a mathematical formula.

NLM expects journals to follow established industry guidelines and best practices, such as those from:

⁹ <https://www.nlm.nih.gov/lstrccommittee/lstrc.html>.

- Committee on Publication Ethics (COPE) - Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by COPE, DOAJ, WAME, and OASPA)¹⁰
- International Committee of Medical Journal Editors (ICMJE) - Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals¹¹
- Council of Scientific Editors (CSE)¹²

NLM will reevaluate a journal if there are article-level issues that appear to be systemic; if there are verifiable concerns about the scientific or editorial quality of the journal content; or if there is a change in a journal's ownership, policies, or practices. The reevaluation process also considers the elements outlined above.

Senator Pat Roberts

- **The 21st Century Cures Act requires NIH to work with USDA and FDA to review policies regarding research with laboratory animals and to make revisions that reduce administrative burden on researchers. Additionally, in March, NIH released an RFI to solicit suggestions for improving coordination with these agencies and completing a review of such regulations.**
 - **What opportunities have you identified to ensure regulations and policies are not inconsistent, overlapping, or unnecessarily duplicative?**
 - **What efforts are currently underway to “cut the bureaucratic red tape” and what future actions can we expect from NIH to ease administrative burden on investigators?**

Answer:

NIH has, for many years,¹³ been concerned about the increasing burden of applying for and reporting on federally-funded research grants, and the costs faced by researchers when complying with requirements. This issue is noted as an area to address in the NIH-Wide Strategic Plan.¹⁴ In March 2018, as part of NIH's implementation of the 21st Century Cures Act,¹⁵ NIH requested public feedback on some proposed approaches to reduce administrative burden on investigators' use of laboratory animals in biomedical research (NOT-OD-18-152¹⁶ and Federal Register Notice 2018-05173).¹⁷ Together with the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA), NIH sought constructive and thoughtful feedback on this topic from individuals, research institutions, professional societies, animal advocacy organizations, and other interested parties. Input was accepted electronically during a 90-day comment period that closed on June 12, 2018. This call helped shed further light on where the community feels that regulations and policies are inconsistent, overlapping, or unnecessarily duplicative, and on possible actions for the agencies to consider in addressing administrative burden.

¹⁰ <https://publicationethics.org/news/principles-transparency-and-best-practice-scholarly-publishing-version-3>.

¹¹ <http://www.icmje.org/recommendations>.

¹² <https://www.councilscienceeditors.org>.

¹³ www.nexus.od.nih.gov/all/2011/11/30/your-input-on-reducing-administrative-burdens-and-costs.

¹⁴ www.nih.gov/about-nih/nih-wide-strategic-plan.

¹⁵ www.congress.gov/bills/114/congress/house-bill/34.

¹⁶ www.grants.nih.gov/grants/guide/notice-files/NOT-OD-18-152.html.

¹⁷ www.gpo.gov/fdsys/pkg/FR-2018-03-14/pdf/2018-05173.pdf.

Using animals in research is critical to scientific understanding of biomedical systems leading to useful drugs, therapies, and cures. It is important to note that, even as NIH strives to identify ways to reduce administrative burden on our supported investigators, we simultaneously aim to maintain the highest standards of integrity and credibility within the biomedical research enterprise. This further extends to NIH continuing to ensure the greatest commitment to the welfare of laboratory animals involved in our supported research endeavors.

Ideas have been collected and analyzed for their relationship to existing statutes, regulations, and policies, as potential approaches to implement in support of the 21st Century Cures Act requirements to reduce administrative burden on investigators in their use of animals. Insights from the community are critical to helping us refine and ensure the final recommendations and implementation plans are appropriate to reducing administrative burden while maintaining our long-standing commitment to the humane care and use of animals in research.

NIH received over 19,000 responses from stakeholders to the RFI. A draft report on the review of the responses and recommendations was posted in the Federal Register on December 7, 2018, after approval by USDA, FDA, and NIH, for a 60-day comment period. The final report is expected in early 2019.

- **I have been happy to support the recent increases in NIH funding, including what was provided in Cures to the Cancer Moonshot project. However, I am interested in how these funds are being spent and how we can best leverage every federal research dollar available.**
 - **Can you provide an update on how recent appropriations and the Cures Act are moving us forward in cancer research?**
 - **How has the Partnership for Accelerating Cancer Therapies helped engage the private sector to make progress in researching and developing new therapies?**
 - **What other steps has NIH taken ensure that data and information from federally- funded cancer research is appropriately shared with other researchers – both public and private – so they can build off of that research?**

Answer:

Using National Cancer Institute (NCI) base appropriations and other appropriations that support the Cancer Moonshot™, NCI continues to support cutting-edge research with the goal of reducing the cancer burden in the United States. In 2016, NCI convened a working group of the National Cancer Advisory Board (NCAB), the Blue Ribbon Panel (BRP)¹⁸ of experts that identified ten areas of research that were poised for acceleration to make rapid progress for cancer patients. These ten cross-cutting research priorities, which include topics such as developing ways to overcome cancer's resistance to therapy and building a national cancer data ecosystem, were chosen because they have the potential to result in contemporary breakthroughs while building the foundation for future innovation.

¹⁸ www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel.

Beginning in fiscal year 2017, NCI issued funding opportunity announcements (FOAs) aimed at encouraging research in these ten areas. As of September 2018, NCI has issued over 50 Cancer Moonshot FOAs.¹⁹ Examples of projects funded through the Cancer Moonshot include:

- The Immuno-Oncology Translation Network (IOTN): Four companion FOAs will support the establishment of the IOTN through the following components:
 - The Cancer Immunotherapy Consortium will be composed of organ-specific Cancer Immunotherapy Research Projects²⁰ and Cancer Immunoprevention Research Projects²¹, creating multi-disciplinary, collaborative teams with the goal of developing improved immunotherapeutic strategies capable of eliminating established cancers or preventing cancers before they occur.
 - The Data Management and Resource-Sharing Center will provide overall support and facilitate collaboration among the IOTN-funded sites, as well as promote scientific outreach with other Cancer Moonshot initiatives and the larger scientific community.²²
 - The Cellular Immunotherapy Data Resource will support a data registry for collecting outcomes of patients receiving cellular immunotherapies.²³
- Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium: Fusion oncoproteins are novel, distinctive proteins that drive cancer growth and survival in a number of childhood cancers. The Consortium, consisting of multidisciplinary teams of childhood cancer researchers, will seek to develop new pre-clinical models of fusion-driven childhood cancer, identify small-molecule therapeutic agents, and deepen scientific understanding of the biology and chemistry of the fusion oncoproteins that drive specific pediatric cancers, with the ultimate goal of developing targeted therapies. NCI also reissued the FOA in summer 2018 so that additional teams will have a chance to compete to be members of the FusOnC2 Consortium.²⁴
- Rare Tumor Patient Engagement Network: Recognizing that patients with rare tumors face many obstacles, including lack of medical expertise about rare tumors in their local community and lack of knowledge of their disease trajectory in the broader oncology community, NCI's Center for Cancer Research, part of the intramural program, launched the Rare Tumor Patient Engagement Network. The Network will leverage the unique resources of the NIH Clinical Center and bring together national and international investigators, patients, advocacy groups and industry with the goals of comprehensively studying rare tumors and providing exceptional patient care.²⁵

Launched in 2017, the Cancer Moonshot-supported Partnership for Accelerating Cancer Therapies (PACT) is a collaboration between NCI and 11 pharmaceutical companies with the goal of rapidly expanding the immunotherapy therapies available to patients.²⁶ PACT's focus, with the benefit of guidance from the Food and Drug Administration, is to identify, develop, and validate robust biomarkers to advance new immunotherapies. Four NCI-supported Cancer

¹⁹ www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding.

²⁰ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-045.html.

²¹ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-046.html.

²² www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-047.html.

²³ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-048.html.

²⁴ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-016.html.

²⁵ www.ccr.cancer.gov/research/cancer-moonshot.

²⁶ www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation.

Immune Monitoring and Analysis Centers, in addition to the Cancer Immunologic Data Commons, are leading the development and implementation of immunotherapy clinical trials that align with PACT goals. To further engage the larger cancer research community, NCI plans to create a pathway for additional researchers to submit candidate clinical trials for inclusion in PACT. NCI is also in the process of developing FOAs to encourage additional partnerships and identify novel biomarkers.

In line with the NCAB BRP recommendation of building a national cancer data ecosystem, NCI is taking a leadership role to break down data silos across the cancer research community while protecting privacy through the development of the Cancer Research Data Commons, which provides data from NCI-supported research to all qualified researchers. Examples include:

1. The Genomic Data Commons²⁷ is a unified system that promotes sharing of genomic and clinical data among researchers. It centralizes, standardizes, and makes accessible data from large-scale NCI programs to provide the cancer research community with a data service supporting the receipt, quality control, integration, storage, and redistribution of standardized cancer genomic data sets in support of precision medicine. Key data sets include The Cancer Genome Atlas²⁸ and the Therapeutically Applicable Research to Generate Effective Treatments Program.²⁹
2. The NCI Cloud Resources,³⁰ developed through contract awards to Broad Institute, the Institute for Systems Biology, and Seven Bridges Genomics, explore cloud-based approaches for enhancing secure data access, collaboration, computational scalability, resource democratization, and reproducibility. They provide infrastructure and a set of tools to access, explore, and analyze molecular data. All three Cloud Pilots have implemented their systems through commercial cloud providers and are collaborating on adopting common standards.
3. The Surveillance, Epidemiology, and End Results (SEER) Program serves as an authoritative source of information on cancer incidence and survival in the United States that collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 30 percent of the US population. SEER is the only comprehensive source of population-based information in the country that includes stage of cancer at the time of diagnosis and patient survival data.³¹
4. The Informatics Technology for Cancer Research program, a trans-NCI grant program, promotes the development of interoperable informatics technologies to allow multilevel data integration of basic science, prevention, epidemiology, and population science data to improve the detection, diagnosis, and treatment of cancer.³²
5. NCI also created a centralized, controlled-access database, called the National Clinical Trials Network/NCI Community Oncology Research Program (NCTN/NCORP) Data Archive. This archive will be used to store and share datasets generated from NCTN clinical trials and make these datasets available in a timely

²⁷ www.gdc.cancer.gov.

²⁸ www.cancergenome.nih.gov.

²⁹ www.ocg.cancer.gov/programs/target.

³⁰ www.cbiit.cancer.gov/ncip/crdc-cloud-resources.

³¹ www.seer.cancer.gov.

³² www.itcr.cancer.gov.

manner, on appropriate terms and conditions, to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work. The archive expands NCI's data sharing activities beyond genetic and genomic data into patient-level clinical trial data.

- **NIH announced the Helping to End Addiction Long-term (HEAL) initiative earlier this year in response to the opioid epidemic. I appreciate your focus on searching for new and non-addictive treatments to pain through a wide array of partnerships. I am also interested in the HEALing Communities study, which includes integrating addiction treatment into primary care settings.**
 - **Why is it important to partner with public- and private-sector stakeholders in researching addiction and pain management?**
 - **How will public-private partnerships help deliver addiction treatment services to patients in more settings, especially in rural areas?**

Answer:

The public health emergency of opioid misuse, addiction, and overdose affects millions of Americans and requires innovative scientific solutions. In April 2018, NIH launched the HEAL (Helping to End Addiction Long-term) Initiative, an aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. This Initiative will build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implementation science to develop and test treatment models, and research to integrate behavioral interventions with medication for opioid use disorder (OUD).

One goal for the HEAL Initiative is to establish public-private partnerships for the development and delivery of new interventions for the treatment of addiction and pain. Partnership with the biopharmaceutical sector responsible for the fabrication and commercialization of new therapies is essential for bringing new medications to patients who need them. In addition, through multiple successful public-private partnerships, NIH has learned that working across sectors allows for the combination of unique expertise and strengths to accelerate progress toward successful therapies for more patients. Toward this goal, NIH is working in partnership with biopharmaceutical companies, the US Food and Drug Administration (FDA), and the Foundation for the NIH (FNIH), to collect and evaluate pharmacological assets for their potential as non-addictive treatment of pain and addiction. These assets, novel agents and repurposed assets deprioritized for reasons other than safety, will be further developed and tested in NIH preclinical development programs and in a new pain clinical trials network.

Another project within the HEAL initiative is the HEALing Communities Study, planned by NIH in partnership with the Substance Abuse and Mental Health Services Administration (SAMHSA). This study will evaluate the impact of implementing an integrated set of evidence based practices for prevention and treatment of opioid use disorders in select communities with high rates of opioid overdose mortality, with a focus on significantly reducing opioid overdose fatalities by 40% in a 3-year period. Targeted areas for intervention include decreasing the incidence of opioid use disorder, increasing the number of individuals receiving medications for opioid use disorder treatment, increasing treatment retention beyond six months, improving

access to recovery support services, and expanding the distribution of naloxone. The study will require partnerships across sectors including primary care, behavioral healthcare, justice settings, and community-based organizations. Partnering with both public and private sector stakeholders leverages the expertise and infrastructure of groups and individuals that work with the affected populations being studied. These stakeholders understand the practical reality of implementing new approaches within the existing system, and are poised to understand the unique needs of both caregivers and individuals with opioid use disorder. From local government, to local health care providers, to the companies that provide lifesaving interventions like the overdose reversal drug naloxone, every partner has a role to play and expertise to contribute. NIH also participates in the Office of National Drug Control Policy's Treatment and Recovery and Rural Opioid Response Interagency Work Groups, which coordinate Administration-wide drug policy efforts.

NIH is committed to implementing interventions, which can be effectively deployed to all communities in need, including rural communities. The National Institute on Drug Abuse (NIDA) has partnered with other public and private entities on projects to implement evidence based approaches to SUD treatment, overdose prevention, and prevention/treatment of infectious disease consequences of opioid injection in rural areas of the U.S, including Appalachia, New England, the Midwest and Pacific Northwest. These projects are supporting the work of state and local communities in developing best-practice responses that can be sustained beyond the life of the grants. One initiative focused on rural regions is co-funded by the Appalachian Regional Commission, the Centers for Disease Control and Prevention (CDC), and SAMHSA, with the aim of stemming the dramatic increase in adverse outcomes associated with increased opioid injection drug use in Appalachia.

Senator Todd Young

- **Currently, researchers and the private sector are looking for outside-of-the-box approaches to combat bacterial infections. Many of these nontraditional approaches are in the preclinical stage – however, there is a need for studies that help bridge the divide between translational science and early-stage development.**
- **How is the NIH helping foster the development of nontraditional antibiotic approaches?**

Answer:

The National Institute of Allergy and Infectious Diseases (NIAID) supports basic research to understand the fundamental biology of disease-causing microbes and the microbial mechanisms used to block antibacterial drugs. NIAID also fosters the development and clinical testing of novel diagnostics, therapeutics (including non-traditional antibiotic approaches), and vaccines to address drug-resistant infections.

NIAID conducts and supports research on the development of innovative alternatives to antibiotics including bacteriophages, microbiome-based approaches, immune-based therapies, and vaccines. NIAID has encouraged research on alternatives to traditional antibiotics for bacterial infections by issuing a targeted funding opportunity announcement that resulted in support for 24 research projects investigating diverse approaches. NIAID also recently partnered with the U.S. Food and Drug Administration to hold a public workshop on the clinical,

manufacturing, and regulatory considerations for live microbiome-based products to prevent, treat, or cure a disease or condition in humans. In addition, NIAID-supported scientists are working to identify protective commensal and symbiotic bacterial strains that could prevent and treat *Clostridium difficile* infection. NIAID intramural investigators also identified a potential host-directed therapy using an antibody to boost the activity of neutrophils, a type of white blood cell, against carbapenem-resistant *Klebsiella pneumoniae*. Furthermore, NIAID is supporting development of vaccines and immunoprophylactics that could help prevent bacterial infections, including a novel vaccine candidate to prevent *Pseudomonas* infections; a new vaccine platform to provide broad protection against pathogenic *Shigella*, *Salmonella*, as well as *Pseudomonas*; and a novel immunoprophylactic against multidrug-resistant (MDR) Gram-negative pathogens.

NIAID also provides support to researchers developing novel antimicrobial products in the form of preclinical and clinical services, including screening tests for antimicrobial activity and access to research reagents to assist in product testing. The NIAID-supported services are intended to help bridge gaps in the product development pipeline and accelerate promising candidates into early-stage development. NIAID has provided these services to further advance the development of new antimicrobial products to more than half of the awardees of CARB-X, a unique public-private partnership led by the Biomedical Advanced Research and Development Authority (BARDA). CARB-X is dedicated to accelerating the development of innovative antibacterial products from target/candidate identification and characterization through Phase I clinical trials, and is currently supporting at least 28 therapeutic candidates, including ten new classes of antibiotics and 11 non-traditional agents.

NIAID will continue to build on the significant progress made through intramural and extramural research, as well as through partnerships with other Federal agencies, academia, and industry, to address the public health threat of antimicrobial resistance. Support for non-traditional antibiotic approaches will remain a critical component of NIAID's efforts to combat antibiotic-resistant infections.

- **Nearly 75 percent of antibiotics in clinical development are based on previously approved classes of antibiotics — there is a need for novel structures and approaches to stay ahead of resistance. Innovative preclinical antibacterial approaches, like CARB-X, are needed. As you know, CARB-X is a global public-private partnership with BARDA, NIH, and other global partners to ensure a robust pipeline of preclinical innovation candidates that protect human health from the most serious bacterial threats.**
- **How is the NIH working as a part of CARB-X to ensure that there are enough preclinical candidates moving on to clinical trials?**

Answer:

The National Institute of Allergy and Infectious Diseases (NIAID) supports a comprehensive research portfolio on antibiotic resistance to ensure a robust pipeline of new approaches to address bacterial infections. These efforts include basic research to aid in the discovery of new antibiotics as well as preclinical studies to advance promising antibacterial products through CARB-X and other programs. NIAID estimates that more than 25 percent of the antibacterial candidates currently in clinical development previously received some form of NIAID support.

NIAID supports the discovery of new antibiotics and antibacterial products through a number of mechanisms, including via unique preclinical and clinical services NIAID provides to researchers in industry and academia. NIAID aims to de-risk antimicrobial product development by offering no-cost services that include screening tests for antimicrobial activity to help identify promising therapeutic candidates as well as access to pathogens, research reagents, and animal models to assist in product testing. NIAID also provides these support services to CARB-X awardees. CARB-X, led by the Biomedical Advanced Research and Development Authority (BARDA), is a critical element in the advancement of solutions to antimicrobial resistance that is currently supporting the development of at least 28 therapeutic candidates, including ten new classes of antibiotics, as well as five diagnostics products. NIAID participates in scientific review of CARB-X applications and provides oversight as a member of the CARB-X Joint Oversight Committee, Scientific Advisory Board, and Milestone Review Board. Since the inception of the program, NIAID has provided technical support and preclinical drug development services to more than half of CARB-X awardees to further advance the development of new products.

In addition to its participation in CARB-X, NIAID is advancing the development of novel antibiotics through several ongoing efforts. For example, NIAID has supported preclinical development and Phase I clinical testing of VNRX-5133, a novel beta-lactamase inhibitor (BLI). VNRX-5133 is the first BLI in clinical development that inhibits all known classes of beta-lactamases – bacterial enzymes involved in resistance to broad-spectrum drugs like penicillin and other members of the beta-lactam class of antibiotics.

NIAID will continue to support the development of antibacterial products in collaboration with academia, industry, and Federal partners. NIAID remains committed to CARB-X and complementary programs to facilitate the development of new antibiotics from discovery and early-stage development through clinical trials.

Senator Mike Enzi

- **I have been following activities at the National Institutes of Health (NIH) related to funding research that involves the introduction of human cells into animal embryos. In 2016, NIH announced that the agency would lift a moratorium on chimera studies, but impose an extra layer of ethical review before approving such research projects. The proposal opened up the possibility of doing such research on non-human primates, which would be a significant change.**
 - **Can you provide an update on implementation of this policy and how you are providing adequate safeguards to prevent research that goes beyond the moral and ethical boundaries for human and animal research?**

Answer:

It is important to note that the NIH Guidelines for Human Stem Cell Research prohibit the introduction of human pluripotent cells into non-human primate blastocyst-stage embryos, as well as prohibit the breeding of animals where the introduction of human pluripotent cells may have led to human sperm or human eggs being produced in the animal.³³ NIH proposed to revise

³³ <https://stemcells.nih.gov/policy/2009-guidelines.htm>.

the Guidelines to expand those prohibitions: to prohibit the introduction of human pluripotent stem cells in pre-blastocyst stage non-human primate embryos; and to expand the prohibition on research involving the breeding of animals to include the introduction of any type of human cell that may contribute to the germ line cells (egg or sperm).

In addition, NIH proposed that applications for certain research projects using chimeras be considered by a steering committee, as an additional level of scrutiny. This analysis would be conducted independent of, and in addition to, the standard peer review procedures for research supported by the NIH. The NIH is considering comments received through the Federal Register Notice to determine the scope of the research to be considered by the steering committee.

The public comment period in response to the “Request for Public Comment on the Proposed Changes to the NIH Guidelines for Human Stem Cell Research and the Proposed Scope of an NIH Steering Committee’s Consideration of Certain Human-Animal Chimera Research,” published in the Federal Register on August 5, 2016, closed on September 6, 2016, with the NIH receiving over 21,000 public comments.³⁴ NIH is in the process of considering all of the public comments. After NIH reaches a final decision, the policy will be announced in the Federal Register and the NIH Guide to Grants and Contracts. Until that time, the moratorium will remain in effect.³⁵

As a strong steward of public funds, the NIH is committed to upholding the highest ethical standards in scientific research and animal welfare. The NIH views this proposed policy framework as a responsible way to provide additional oversight and new limitations in an area of research that is very promising but requires careful guidance.

Senator Susan Collins

- **Last year, Bill Gates announced that he is “digging deep” into Alzheimer’s research and has suggested that we need more data sharing to increase chances of finding an Alzheimer’s breakthrough. What are the key impediments to better data sharing and what steps is NIH taking to facilitate sharing?**

Answer:

NIH supports a number of critical projects relevant to Alzheimer’s disease and related dementias (AD/ADRD) that conduct standardized data collection, including data from long-standing longitudinal cohorts. These datasets are treasure troves of data, information and knowledge that can be analyzed in new ways; we anticipate that expanding access to and use of these data will accelerate the pace of discovery, help us identify new treatment targets, and even speed recruitment to clinical trials. However, challenges to widespread data-sharing exist:

- We need to sustain and expand our efforts to modernize existing and develop new big data infrastructure to maximize accessibility and usability of data.

³⁴ https://grants.nih.gov/grants/rfi/responses_57.cfm.

³⁵ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-158.html>.

- We need to facilitate data-sharing from privately/industry-sponsored clinical trials, including data from those that had negative findings.
- We need to develop new analytical methods development, including artificial intelligence and machine learning.
- We need to train, recruit, and retain researchers with various types of data science expertise.
- We increasingly need web-based interfaces and data mining and visualization tools that enable researchers with various skill sets and expertise to work with complex datasets.
- We need to work with funding agencies, academic institutions, and publishers to develop and implement policies that support rapid and broad data-sharing and participation in team science. These policies must cover all forms of data—raw and processed data, analytical results, and methods—to enable wide use of publicly and privately funded data for both discovery and replication research, while protecting patients' privacy.

Many National Institute on Aging (NIA) AD/ADRD initiatives include innovative development, management, and widespread sharing of “big data” sets, including:

- **Alzheimer's Disease Centers (ADC) Program:** From 2005 to the present, ADCs have been contributing data to a **Uniform Data Set (UDS)** using a prospective, standardized, and longitudinal clinical evaluation of the participants in the NIA's ADC Program. Today, there are 30 ADCs that annually collect data on approximately 40,000 people with cognitive statuses along the continuum from cognitively normal to dementia, and with various types of dementia. In addition, a less expansive data set is available with information from ADC enrollees (both with and without dementia) who were followed between 1984 and 2005. Neuropathology data are available for approximately 16,000 participants who died and underwent autopsy; UDS data are associated with about a third of those. All of these data are available, with stringent privacy controls, through the National Alzheimer's Coordinating Center (NACC).
- **Alzheimer's Disease Neuroimaging Initiative (ADNI):** ADNI provides researchers around the world with high-quality imaging and other biomarker data as they work to define the progression of AD. Data are broadly available, without delay or embargo, via a dedicated data sharing platform.
- **NIA Genetics of Alzheimer Data Storage Site (NIAGADS):** NIAGADS shares data from genomic studies of late-onset AD, including genotyping and sequencing data; extensive phenotype data; and summary statistics from published genetic studies.
- **The Accelerating Medicines Partnership – Alzheimer's Disease (AMP-AD):** AMP-AD provides an infrastructure for rapid and broad data-sharing from multiple NIA/NIH supported epidemiologic studies and brain banks. Data-sharing is enabled through the **AMP-AD Knowledge Portal**, an informatics platform providing access to rich molecular datasets and data on clinical and pathologic phenotypes from several thousand subjects across all stages of AD. Importantly, the portal provides access to raw and processed data as well as analytical results, enabling researchers from the academic and industry sectors to analyze the data in new ways. Researchers are using these invaluable data resources to discover and better understand AD/ADRD-specific disease pathways, to identify novel therapeutic targets and biomarkers, and to make better predictions about drug repurposing and combination therapy development.

- **Behavioral and Social Research Data Collection Activities:** NIA also supports many large longitudinal cohort studies that include cognitive measures and, beginning in FY2016, assessments of dementia status in the U.S. Health and Retirement Study that are, derived from a protocol (the Harmonized Cognitive Assessment Protocol, or HCAP) that is now being used also in representative population studies in Mexico, England, and India. All of the HCAP projects are still collecting data, and all are creating data resources that will be freely available to other qualified researchers. NIA also encourages and funds linkages to Medicare and Medicaid data, which has allowed analyses of health and long-term care utilization and outcomes.

An important feature of all these data resources is the transparency and access of the data, including measures for secure management of the information. Efforts are underway to further integrate data sets across NIA-funded centers and consortia working on AD.

- **The opioid epidemic has shown no signs of abating. New CDC data has shown that in Maine, the crisis has actually worsened, with drug-related overdoses claiming the lives of 407 Mainers last year. We have dedicated billions of dollars to stem the tide, and we are anxiously awaiting results. I was encouraged earlier this month to hear about an NIH-funded study published in the journal Science that found that a simple behavioral nudge reduces prescribing practices. In this study, researchers at the University of Southern California found that sending physicians letters to inform them about the overdose death of one of their patients, resulted in a nearly 10-percent reduction of the number of opioids they prescribed. This study illustrates a small and inexpensive method to reduce the number of opioid prescriptions written, which can lead to large and meaningful difference for Americans. What steps is NIH taking to translate these and other promising research findings into practice?**

Answer:

NIH believes that finding ways to translate promising research findings into medical practice is an important part of its mission. On the topic of opioid use disorder (OUD), the two main areas of focus are in engaging healthcare providers about the latest evidence and conducting real-world trials of implementing new opioid treatment practices into the health care system.

The NIH supports the Centers of Excellence in Pain Education (COEPs), which act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, pharmacy and other schools to enhance and improve how health care professionals are taught about pain and its treatment. Co-sponsored by 8 NIH Institutes, Centers, and Offices, including the National Institute on Drug Abuse (NIDA), the COEPs provide an opportunity to not only develop educational materials, but also to test and iteratively improve them in order to find the best way to disseminate such critical information.

In addition, at NIDA, the NIDAMED initiative helps clinicians acquire the tools and skills needed to incorporate drug abuse screening and treatment into their clinical practices. For example, NIDAMED released an online Continuing Medical Education course on “Adolescent Substance Use and RX Misuse,” which reached over 17,000 clinicians in 11 months. NIDAMED

also helped to facilitate a national partnership between the National Institutes of Health and the American Dental Association on ways to enhance and support dentistry's role in preventing opioid misuse. NIDAMED is a key tool for engaging and educating clinicians, and plans are underway to continue and expand these efforts.

NIDA's Clinical Trial Network (CTN) also acts as a hub for exploring the implementation of promising interventions for drug addiction. The CTN comprises 13 research nodes with 25 principal investigators affiliated with academic medical centers and large health care networks, two research coordinating centers, and more than 240 community anchored treatment programs and/or medical settings in over 40 States plus the District of Columbia and Puerto Rico, allowing it to test interventions on a large scale in real-world settings. The CTN is conducting studies to evaluate strategies for integrating OUD screening and treatment into emergency departments, pharmacies, primary care clinics, and American Indian communities. The CTN has also supported studies to integrate OUD care into electronic health record (EHR) systems, to capture important data for research on substance use in EHR systems for primary care and emergency departments and is currently developing and testing a clinical decision support (CDS) tool for OUD care for use in EHR systems. These studies help to discover the most effective ways to help physicians make informed choices about patients with OUD and build a healthcare system that supports those choices. A comprehensive resource repository of CTN findings is accessible to clinicians, researchers, and policy makers through the CTN dissemination library.

Through the Helping to End Addiction Long-term (HEAL) Initiative, NIH has a number of research projects planned to address the translation of promising research findings into practice. An effort focused on pragmatic and implementation studies for the management of pain, currently in the planning stages, support research embedded in health care systems to collect data in "real world" settings. It will also assess the impact of implementing interventions to improve pain management through better adherence to evidence-based guidelines such as the CDC guideline for the management of chronic pain. The results from these studies will inform clinicians, patients, and health care policy, and change in pain management practice.

NIH has also partnered with the Substance Abuse and Mental Health Services Administration (SAMHSA) to plan the HEALing Communities Study. This study will evaluate the impact of implementing an integrated set of evidence-based practices for prevention and treatment of opioid use disorders in select communities with high rates of opioid overdose mortality, with a focus on significantly reducing opioid overdose fatalities by 40%. The study will test the integration of evidence-based interventions for opioid misuse, opioid use disorder across multiple settings, including primary care, behavioral health, and justice, and community resources such as police departments, faith-based organizations, and schools. The evidence we generate will help communities nationwide address the opioid crisis at the local level.

NIH is committed to not only increasing our fundamental understanding of living systems, but to translating that understanding into changes that have an impact on medical practice and the health of the nation. By working to transmit the latest evidence to clinicians, and by testing new ways to support physicians and other health professionals in making the best possible choices for their OUD patients, NIH is actively supporting the process of turning cutting-edge research into life-saving practice.

Senator Richard Burr

- **Dr. Collins’ testimony describes the potential of precision medicine and the efforts underway to better understand the underlying genetic information that will allow researchers to harness this potential. Along the way, the NIH, and other research institutions may have access to the genetic information of many Americans. How does the NIH protect this sensitive information?**

Answer:

The *All of Us* Research Program takes seriously the trust our participants place in us. Our values state that “security and privacy will be of highest importance.” The program’s privacy and security policies are built upon the Precision Medicine Initiative (PMI) Privacy and Trust Principles³⁶ and the PMI Data Security Policy Principles and Framework.³⁷ These documents, and the guidelines therein, apply to all organizations participating in the *All of Us* Research Program.

All of Us uses the most up-to-date industry standards and practices to prevent security breaches. While no one can offer a 100% guarantee that a security breach will not happen, we are doing everything in our power to prevent this from occurring. We implement security controls that have been assessed against federal standards and industry best practices. Our security controls are applied using a layered defense within enterprise grade cloud platforms that have undergone extensive testing and validation through the Federal Risk and Authorization Management Program (FedRAMP). The program enlists teams of experts to establish safeguards and conduct rigorous security testing, including ensuring that *All of Us* security practices meet the program’s requirements, as well as all federal, state, and local laws and regulations around safeguarding participant data. They conduct ongoing rigorous security testing, including security controls testing, vulnerability scanning, and penetration testing.

In addition to adhering to the highest standards of information security, the program also leverages all applicable legal and regulatory privacy tools. The program is covered by a Certificate of Confidentiality, which prohibits disclosure of identifiable, sensitive information collected during research, unless disclosure falls within a statutory exception. Furthermore, *All of Us* requires that awardees and subawardees use any and all available legal measures to oppose legal requests for participant identities or data to protect participants’ privacy, including through certificates of confidentiality.³⁸ HIPAA’s Privacy, Security, and Breach Notification Rules apply to *All of Us* activities under the PMI to the extent the entity conducting PMI activities is considered a HIPAA-covered entity (for example, a health care provider) or a business associate. The program’s privacy and security postures are also compliant with 42 CFR Part 2 in order to afford appropriate protection to sensitive information regarding mental health and substance use.

In addition, *All of Us* uses unique data curation and access models that help prevent unintended

³⁶ <https://allofus.nih.gov/about/program-overview/precision-medicine-initiative-privacy-and-trust-principles>.

³⁷ <https://allofus.nih.gov/about/program-overview/precision-medicine-initiative-data-security-policy-principles-and-framework-overview>.

³⁸ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html>.

use or abuse of participant data. All interactions with the *All of Us* data resources will occur in a secure, cloud-based data enclave; researchers will conduct all analyses with individual-level data in workspaces within that enclave and are prohibited from downloading individual-level data. Resource data will be stratified, based on sensitivity, into access tiers. The public tier contains aggregate statistics, the registered tier holds individual-level data with a low risk of participant reidentification or misuse, and the controlled tier houses more sensitive individual-level data. This stratification may be adapted over time to reflect the current standards and technological capabilities.

All individuals wishing to access *All of Us* data resources at the registered and controlled levels must apply for that access. The application process includes identity verification and privacy and ethics training. Users must also sign the *All of Us* Data Use Agreement, which contains the User Code of Conduct. Violation of the Data Use Agreement will be subject to penalty, ranging in severity based on the scope and intent of the infraction. The *All of Us* Resource Access Board will be charged with overseeing review of user applications.

Researchers will be required to append descriptions of their intended research, as well as the types of data they use, to their project workspaces. These descriptions will be subjected to periodic audit and will also be posted publicly so that anyone can flag suspicious or potentially non-compliant research for review by the *All of Us* Resource Access Board.

- **On August 23, the NIH announced a new working group of the Advisory Committee to the Director tasked with developing methods to improve the reporting of sources of research funding, mitigating the risk to intellectual property security, and considering steps to protect the integrity of the peer review process. How will the efforts of this working group incorporate considerations related to the storage and security of, and access to, the genetic information of Americans provided to the NIH for research purposes?**

Answer:

NIH and the U.S. biomedical research community at large have a vested interest in the integrity of U.S. biomedical research. Breaches of trust and confidentiality are unacceptable and inconsistent with NIH's guiding principles of scientific excellence, research integrity, and fair competition. NIH expects everyone involved in NIH-supported research—both domestic and foreign—to promote research integrity in fulfillment of NIH's research mission.

NIH is working with other government agencies and the broader biomedical research community to mitigate inappropriate foreign influences on research integrity, while maintaining appropriate collaborations with scientists across the globe. One step to achieve this is through establishing the Advisory Committee to the NIH Director (ACD) Working Group on Foreign Influences on Research Integrity.³⁹ The ACD working group will be focused on promoting research integrity and, through the ACD, helping NIH to further support NIH's existing stringent policies guiding research.

While not charged specifically with discussing the security of genetic information, the ACD

³⁹ <https://acd.od.nih.gov/working-groups/foreign-influences.html>.

working group may review existing NIH best practices and policies that ensure the broad and responsible security and sharing of genomic research data. Reflecting our serious commitment to this issue, NIH has established many policies to promote security, storage, and responsible access to genetic data provided by research participants involved in clinical research. Specific examples of policies and best practices that NIH can point to include:

1. NIH Grants Policy Statement Section 2.3.12⁴⁰ – recipients of NIH funds have a responsibility to protect sensitive and confidential data as part of proper stewardship of federally funded research and take all reasonable and appropriate actions to prevent the inadvertent disclosure, release, or loss of sensitive personal information. Further, as stated in Section 4.1.4.1 of the NIH GPS,⁴¹ recipients are required to protect the privacy of individuals who are subjects of research that collect or use identifiable, sensitive information (see also the NIH Certificates of Confidentiality Policy.⁴²
2. NIH Genomic Data Sharing Policy⁴³ (NIH Grants Policy Statement Section 2.3.7.10)⁴⁴ – NIH-designated data repositories use strict security provisions, including multiple firewalls, separate servers, and data encryption protocols to protect the data. Those seeking access to such data must agree to specific terms of use, including storing the requested data securely and not sharing with third parties. Further, GPS Section 8.2.3.3 also references the NIH Security Best Practices for Controlled Access Data Subject to the NIH Genomic Data Sharing Policy.⁴⁵
3. The NIH's *All of Us* Research Program stipulates as part of its guiding principles that security and privacy of participants and their data will be of highest importance.⁴⁶ Consistent with the program's data security policy and principles, award institutions select the security framework that adequately addresses the security risks they face. Furthermore, the framework encourages institutions to have security programs that assess cybersecurity and data security performance, as well as physical and environmental controls.⁴⁷

⁴⁰https://grants.nih.gov/grants/policy/nihgps/html5/section_2/2.3_application_information_and_processes.htm#tocpath=2%20The%20National%20Institutes%20of%20Health%20as%20a%20Grant-Making%20Organization%7C2.3%20Application%20Information%20and%20Processes%7C12#2.3.12_Protecting_Sensitive_Data_and_Information_Used_in_Research...33

⁴¹ https://grants.nih.gov/grants/policy/nihgps/html5/section_4/4.1.4_confidentiality.htm#Confidentiality.

⁴² <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html>.

⁴³ <https://osp.od.nih.gov/scientific-sharing/genomic-data-sharing>.

⁴⁴

https://grants.nih.gov/grants/policy/nihgps/html5/section_2/2.3_application_information_and_processes.htm#tocpath=2%20The%20National%20Institutes%20of%20Health%20as%20a%20Grant-Making%20Organization%7C2.3%20Application%20Information%20and%20Processes%7C2.3.7%20Policies%20Affecting%20Applications%7C10#2.3.7.10_NIH_Genomic_Data_Sharing...18.

⁴⁵ https://grants.nih.gov/grants/policy/nihgps/html5/section_8/8.2.3_sharing_research_resources.htm.

⁴⁶ <https://allofus.nih.gov/about/program-overview/precision-medicine-initiative-data-security-policy-principles-and-framework-overview>.

⁴⁷ <https://allofus.nih.gov/about/program-overview/precision-medicine-initiative-data-security-policy-principles-and-framework-overview/achieving-principles-through-precision-medicine-initiative-data-security-policy-framework>.

Ranking Member Patty Murray

- In June, the National Academies of Science, Engineering, and Medicine (NASEM) released a report on the sexual harassment of women in science, finding that three in five women in academia have experienced sexual harassment at work. The report suggests that agencies invest in sexual harassment at an amount that is at least equal to investments made to address scientific misconduct.
 - Earlier this summer, U.S. Representative Rosa DeLauro and I wrote to you to learn more about the steps NIH is taking to address harassment both in the NIH workplace and in NIH-funded research institutions in light of the NASEM report. As mentioned in the letter, the NASEM report commends a National Science Foundation (NSF) proposed policy that would require institutions to report to NSF when any investigator or grant personnel on an NSF grant is found guilty or placed on administrative leave due to a harassment finding or investigation. This gives NSF the opportunity to respond to the incident, including suspending or terminating an award, as the agency deems appropriate.
- Your response provides a useful overview of NIH's existing mechanisms and indicates that you are exploring further collaboration with the Department of Health and Human Services' Office for Civil Rights. Could you share more detail on this collaboration and whether it will result in policies similar to those proposed by NSF? Does NIH intend to implement a similar reporting requirement, and if not, why not?
 - The Academies' report outlines institutional "culture" and environmental factors that are major contributors to the level of sexual harassment and gender discrimination within an institution, including the "perceived tolerance for sexual harassment," "male-dominated work settings," and hierarchical power structures. Since NIH allocates roughly 80 percent of its budget to extramural research awards, your agency clearly has significant leverage to influence its grantee institutions. What is NIH doing to influence and encourage its grantee institutions to ameliorate these issues?

Answer:

The HHS Office for Civil Rights (OCR) enforces Title IX for the Department. (This is unlike NSF, which we understand to house both Title IX enforcement and grant-making authorities.) While NIH cannot enforce Title IX, NIH can monitor and audit grantee institutions for compliance with terms and conditions of awards, including the requirement to submit an Assurance of Compliance (AoC) certification pertaining to Title IX (Section 4.1.2.2 of the NIH Grants Policy Statement). A collaboration with OCR could allow us a better understanding of OCR's data, e.g., we can explore the prospect of conducting routine queries on whether an Assurance of Compliance for the institution is on file, among other considerations.

We do not expect that further collaboration with OCR would result in a reporting requirement where institutions would be required to specifically disclose if an investigator or other grant

personnel are found by the institution to have violated institutional policies or are placed on administrative leave due to a harassment finding or investigation.

To clarify, both NSF and NIH require institutions to report if there is a change of PI on an award for any reason. It is our understanding that NSF has now added that their awardee institutions must specifically disclose the reason of administrative leave when it is due to a harassment finding or investigation. In addition, it is our understanding that NSF now asks their awardee institutions to report any findings of sexual harassment, even those that did not result in administrative actions. With this knowledge, we understand that NSF intends to respond to this information by “substituting or removing principal investigators or co-principal investigators, reducing award funding, and -- where neither of those options is available or adequate -- suspending or terminating awards.” NIH can reach a similar outcome, though we take a different approach by asking questions that directly pertain to the impact on NIH-funded research. When a grantee institution requests prior approval for a change in status of senior/key personnel on an NIH award, we can ask more about who will be carrying out the work, to ensure that they are highly qualified and that NIH is otherwise willing to approve the substitution, but we do not require institutions to disclose the specific reason why someone is no longer on the grant. We can ask what the university is doing to ensure that the workplace is safe but cannot require institutions to specifically disclose how an individual employee has been punished by the institution for (alleged) violations of that institution’s protocol. Once we do know about a change in status of senior/key personnel that has impacted NIH-funded research, e.g., that a PI has been placed on restrictions (due to a finding or investigation of sexual harassment or otherwise), we can take similar actions as NSF as further described below.

We are taking sexual harassment very seriously and are actively using the levers and authorities we currently have to directly address allegations of sexual harassment. When we are notified of, or find out about, allegations or findings of harassment that impact NIH-funded research, such as a PI put on administrative leave without access to their lab, we thus have an entry into inquiry about the grant. We can then request:

- information on the institution’s policy and process (protocol) for reporting and managing allegations and/or findings of Title IX violations.
- a plan for addressing any reported or perceived deficiencies in that protocol, given the (potential) impact on NIH-funded research.

We also raise specific concerns to the institution (usually the Vice President of Research) reinforcing the connection to active or pending NIH funding, and requesting additional information and communication within a designated timeline.

If plans for resolving deficiencies in policies/protocol are insufficient or not submitted within the time frame NIH specifies, we can then consider actions that may include withholding support from a grantee institution until a corrective action plan is accepted and implemented.

As aforementioned, our grantee institutions must alert us about changes in status of senior/key personnel, such as when a PI is placed on leave or his/her employment has been terminated. When this occurs, NIH can take several actions including approving a new lead PI recommended by the grantee as scientifically appropriate or suspending or terminating the grant. Generally, NIH views

a replacement of lead investigator as the best course of action, when possible, to allow scientific progress of a peer-reviewed project, and in consideration of all involved in the circumstances, such as employees and trainees, including those affected by harassment, who participate on the grant and whose careers rely on this work.

We recognize this is insufficient for confronting the widespread gender discrimination described in the NASEM report. To further consider the recommendations from the NASEM report, a high level working group of the Advisory Committee to the NIH Director (ACD) is being assembled to explore the prospect, ultimately communicated through the ACD, of systemwide changes to culture and climate needed to prevent harassment and gender discrimination, and actions that can be taken by research institutions, and NIH. The roster and charge of this working group will be announced publicly at the December ACD meeting.

- **The report also points out that federal agencies can do more to reward and incentivize institutions that are proactively and successfully taking steps to reduce and prevent sexual harassment. In what ways is NIH considering this recommendation?**

Answer:

To incentivize institutions to take action, we have added language to our funding opportunity announcements to emphasize the need for a safe working environment for NIH-funded research. For example, in our conference grant funding opportunity announcement, revised in 2016, we explicitly state our expectation that conference organizers take steps to maintain a safe and respectful environment for all attendees. In an August 2018 NIH Guide Notice (NOT-GM-18-040),⁴⁸ NIGMS, which funds the majority of NIH institutional training grants (T32 grants), reaffirmed that training grant applications should address safe working environments, and specifically added that the support letter from an institutional leader should discuss actions for *“ensuring that proper policies, procedures, and oversight are in place to prevent discriminatory harassment and other discriminatory practices and to appropriately respond to allegations of such discriminatory practices, including providing any required notifications to NIH (e.g., requesting NIH’s prior approval of a change of PD/PI status; see NOT-OD-15-152 and NOT-OD-18-172)”*

- **NIH has sought efforts to elevate the work of young researchers who might not otherwise get recognized for their contributions to science. The Next Generation Researchers Initiative Working Group (NGRIWG) points to Early Independence Awards (EIAs) and several other awards as examples of new initiatives that may prioritize promising scientists over the most exciting science as a strategy to promote and protect early stage and other investigators at risk of losing funding. In May, an NIH panel reviewed EIA candidates. Despite the success of these efforts to elevate young scientists, an article in *Science* revealed that, while male researchers constituted a larger portion of the applicant pool for EIAs than females, men have received these awards at rates that exceed their disproportionate representation. In 2015, according to *Science*, men won 81 percent of EIAs, while they represented**

⁴⁸ <https://grants.nih.gov/grants/guide/notice-files/NOT-GM-18-040.html>.

only 58 percent of the applicant pool. The article also expounds that “men appear to be favored throughout the selection process. Applicants are nominated by their institutions, which tend to put forward more men; and men disproportionately are chosen as winners.” Additionally, the review panel was apparently chaired by a researcher who had been suspended from his institution due to sexual harassment allegations.

- What is NIH doing to ensure that a diverse array of scientists are getting fair and equal access to and opportunities for these types of awards and other research funding?

Answer:

The NIH is keenly aware of the importance and value in having a diverse workforce. Thus, questions regarding diversity (including gender, race, ethnicity, and institutional) in the Common Fund’s High-Risk, High-Reward (HRHR) Research program⁴⁹, which includes the Early Independence Award (EIA), prompted the NIH Director to convene an NIH Advisory Committee to the Director working group on the HRHR program in February 2018. This working group is in addition to the NGRIWG referenced above and is focused specifically on the Common Fund’s HRHR awards, including EIA. The working group is tasked with analyzing and evaluating the diversity within the program and, if shortcomings are found, proposing steps the NIH might take to overcome these shortcomings while maintaining a focus on supporting the best science. Findings and recommendations will be presented next year.

The HRHR program supports two initiatives for early career scientists. The NIH Director’s New Innovator Award supports scientists with innovative ideas who are within ten years of completing their terminal research degree or clinical training and who have not yet received substantial NIH funding. EIA supports research by junior scientists ready to skip postdoctoral training and immediately pursue independent research.

Analyses of the New Innovator Award and EIA have found statistically significant gender differences between the percentage of female applicants and awardees in both programs. From 2007 (the beginning of the initiative) to 2018, 31% of New Innovator applicants were female, but 35% of awardees were female. Given the large number of applicants and awardees for the New Innovator Award, this difference is statistically significant and indicates that female applicants are highly competitive and successful. Regarding EIA, from 2011 (the beginning of the initiative) to 2017, 40% of EIA applicants and 26% of awardees are female, indicating a statistically significant greater representation of male EIA awardees. However, if the data for 2018 are included, the difference between female applicants and awardees is no longer statistically significant with 39% of applicants and 28% of awardees being female. However, the relatively small number of applications and awards for the EIA program contribute to this lack of statistically significant difference.

As one measure to guard against potential gender bias with the EIA review process, the 2019 competition was changed to eliminate the interview component pending possible additional recommendations from the Advisory Committee to the Director working group. Literature on gender bias suggests women may be judged more harshly and unfairly during interviews than

⁴⁹ <https://commonfund.nih.gov/highrisk>.

men. For EIA, in most years from 2011 to 2017, a drop in the percent of females was observed between the interview and the award stage. Now the EIA review will follow a similar process as the New Innovator Award, consisting of expert reviews followed by a panel discussion with broad-thinking scientists.

The chair of the EIA interview panel for the last several years recently was accused of sexual harassment. Unfortunately, the NIH was unaware of these accusations until after the interviews were conducted. This individual will no longer be serving as an NIH reviewer. However, examination of patterns of female applicants, finalists, and awardees with and without him as chair indicates no discernible bias introduced by his participation.

Beyond the Common Fund's HRHR program, many other efforts at NIH are underway to ensure that a diverse array of scientists are getting fair and equal access to and opportunities for research funding. The Common Fund also supports the Diversity Program Consortium⁵⁰, a national collaborative with the overarching goal of developing, implementing, assessing, and disseminating innovative, effective approaches to research training and mentoring. The National Institute of General Medical Sciences (NIGMS) manages the Diversity Program Consortium, and is a leader in supporting programs that foster research training and the development of a strong and diverse biomedical research workforce. The NIGMS seeks to enhance the diversity of the biomedical research workforce by supporting individuals from a variety of backgrounds at multiple training and career stages in a range of institutions and educational settings across the country. Diversity enhancing programs include the Initiative for Maximizing Student Development (IMSD)⁵¹, the Research Initiative for Scientific Enhancement (RISE)⁵², the Maximizing Access to Research Careers - Undergraduate Student Training in Academic Research (MARC U-STAR)⁵³ program, as well as three programs that support trainees across critical transitions including the Bridges to the Baccalaureate program⁵⁴, the Post-baccalaureate Research Education Program (PREP)⁵⁵, and the Bridges to the Doctorate program⁵⁶. The NIGMS funds postdoctoral diversity enhancing programs through the Institutional Research and Academic Career Development Awards (IRACDA)⁵⁷. Many other NIH Institutes and Centers support additional efforts to diversify the scientific workforce. The NIH's Scientific Workforce Diversity Office⁵⁸ coordinates across NIH to lead efforts to diversify the national scientific workforce and expand recruitment and retention.

- **Concerning reports and inspections at the NIH Clinical Center led you to create a “Red Team” of external investigators to advise how best to get the Center into much-needed compliance with standards for patient safety standards and operations. The Red Team’s report cited substantial operational issues with patient safety, regulatory compliance, and leadership across institutes. Based on**

⁵⁰ <https://www.nigms.nih.gov/training/dpc/Pages/default.aspx>.

⁵¹ <https://www.nigms.nih.gov/Training/IMSD/Pages/default.aspx>.

⁵² <https://www.nigms.nih.gov/Training/RISE/Pages/default.aspx>.

⁵³ <https://www.nigms.nih.gov/Training/MARC/Pages/USTARawards.aspx>.

⁵⁴ <https://www.nigms.nih.gov/Research/Mechanisms/Pages/BridgesBaccalaureate.aspx>.

⁵⁵ <https://www.nigms.nih.gov/Training/PREP/Pages/default.aspx>.

⁵⁶ <https://www.nigms.nih.gov/Research/Mechanisms/Pages/BridgesDoctoral.aspx>.

⁵⁷ <https://www.nigms.nih.gov/Training/CareerDev/Pages/TWDInstRes.aspx>.

⁵⁸ <https://diversity.nih.gov>.

the report's recommendations, you announced a reorganization of the Center and investments to update out-of-date infrastructure. Please provide an update on NIH's implementation of the Red Team's recommendations, as well as agency-wide efforts to ensure patient safety remains a top priority.

Answer:

Since the release of the Red Team report, the Clinical Center and the NIH have worked to implement the recommendations made to enhance patient safety and regulatory compliance. In order to best fortify a culture and practice of safety and quality, we have established a new Clinical Center Research Hospital Board, as well as created a new Chief Executive Officer position to drive a culture of patient safety and hired a new Chief Operating Officer. Additionally, the Clinical Center has made significant changes to the Pharmacy, such as closing the Pharmaceutical Development Section – the location of the sentinel event mentioned in the report. We also completed a turnover of pharmacy leadership while expanding staffing to ensure patient safety. The Clinical Center also implemented a number of organization-wide changes, including the creation of daily patient safety huddles open to all clinicians and attended by senior leadership and staff from the institutes and hospital. We have also worked to instill a culture of safety and care through providing more resources to the Office of Patient Safety and Clinical Quality and creating a new and improved safety tracking and recording system.

Strengthening leadership for clinical care quality, oversight, and compliance has also been a focus of our efforts, and we have thus created the Office of Research Support and Compliance within the Clinical Center. We also worked to enhance oversight and compliance through pursuing trans-NIH education efforts concerning the importance of compliance best practices. To that end, we have performed both internal and outside independent compliance audits across the Clinical Center and have purchased a unified IT system for all institutes to enhance compliance and compliance oversight. Lastly, we are in the process of centralizing all institutional review board operations to standardize and oversee research processes.

In tandem with these NIH and CC-level programs, we have also made significant changes to the activities in our Pharmacy. In addition to the above personnel changes to the Pharmacy, we have engaged Duke University for expertise in sterile processing and opened a new intravenous admixture unit to ensure the creation of superior medical products. The Clinical Center also leverages this expertise to advise, audit, and inspect our facilities, standard operating procedures, documentation, and operations to ensure compliance with the highest industry standards. We have also redone our standard operating procedures and re-trained staff to meet current Good Manufacturing Practice (cGMP) standards. Not only do we hold our Pharmacy to these standards, we also apply them to areas like the cell processing facilities in the Department of Transfusion Medicine. Furthermore, we have established a Sterile Products for Human Administration Committee that reviews all preparation of injectables, as well as products procured from external sources. All of these changes have been made to protect our patients, in keeping with the recommendations of the Red Team report. It should be noted that determination was made in the August 2017 NIH Federal Managers' Financial Integrity Act FY 2017 report that regarding "Operational and Regulatory Deficiencies within the Clinical Center: As of July 14, 2017, NIH has implemented all eleven recommendations outlined in the

ACD Working Group's publicly available report, 'Reducing Risk and Promoting Patient Safety for NIH Clinical Intramural Research,' issued in April 2016. The implemented recommendations were aimed at enhancing the organization, financing, and management of the Clinical Center, improving the quality of patient care, and reducing risks associated with clinical research and research-related activities. NIH considers the corrective action plan to be completed."

The Red Team report made a total of eleven recommendations (Appendix I), and the CC and NIH have together implemented measures to address all of them. We have taken the recommendations of the team seriously and undertaken great efforts in the last two years to protect our patients. April 2018 marked the 2-year anniversary of the Red Team Report and the CC Executive team comprehensively evaluated themes, findings and recommendations in the report to conclude that all recommendations were met. Patient safety in a research environment is and will remain our top priority, and we are dedicated to continuing to ensure patient safety, regulatory compliance, and leadership in the future.

APPENDIX I

11 RECOMMENDATIONS FROM RED TEAM REPORT

THEME 1: FORTIFY A CULTURE AND PRACTICE OF SAFETY AND QUALITY

1. Adopt new CC mission & values statements that reflect the critical linkage & synergism of science & safety.
2. Establish a Research Support and Compliance Office.
3. Establish systems to monitor and enforce safety and quality standards.
 - a. Implement strengthened reporting systems.
 - b. Enhance accountability by establishing metrics for quality and safety measures.

THEME 2: STRENGTHEN LEADERSHIP FOR CLINICAL CARE QUALITY, OVERSIGHT, AND COMPLIANCE

4. Establish a hospital board.
5. Enhance clinical research leadership authority and responsibility.
 - a. 5a. Centralize authority for intramural clinical research.
 - b. 5b. Clarify the responsibilities of CC leadership.
 - c. 5c. Integrate patient safety in individual performance plans.
6. Establish a Clinical Practice Committee (CPC).
7. Identify and eliminate potential gaps among clinical services.

THEME 3: ADDRESS STERILE PROCESSING OF ALL INJECTABLES AND THE SPECIFICS OF THE SENTINEL EVENT

8. Do not rebuild the PDS in the CC.
9. Create a prioritization and governance system for sterile products.
 - a. Centralize authority for intramural clinical research.
 - b. Enhance resource sharing across ICs.
10. Ensure that the IVAU and non-sterile PDS are fully remediated.
11. Assess all facilities at NIH producing sterile materials.

- **In June 2018, you announced that NIH would cease funding the Moderate Alcohol and Cardiovascular Health (MACH) trial after internal investigations revealed improper coordination between NIH scientists and the alcohol industry in the design and funding of the study. You simultaneously announced plans to conduct a thorough review to ensure such violations of policy do not occur elsewhere in the agency. What are the agency's findings from that internal review? How is the agency communicating with its researchers to ensure compliance with solicitation guidelines?**

Answer:

In June 2018, NIH announced it will end funding to the Moderate Alcohol and Cardiovascular Health (MACH) trial.⁵⁹ Informed by recommendations⁶⁰ of the Advisory Committee to the Director (ACD)⁶¹, this decision was based on concerns about the study design that cast doubt on its ultimate credibility, along with significant process irregularities identified in the development of the funding opportunities, which undermined the integrity of the research process.

Additionally, a preliminary report from the NIH Office of Management Assessment determined that a small number of National Institute of Alcohol Abuse and Alcoholism (NIAAA) employees violated NIH policies in soliciting gift funding and circumvented standard operating procedures designed to ensure a fair competition for NIH funding. These policy violations were committed by NIAAA employees prior to the involvement of the Foundation for the National Institutes of Health (FNIH), and the review found that the FNIH conducted its role appropriately. The FNIH manages the solicitation of funds by private donors for NIH research projects with appropriate firewalls.

NIH is determined to make sure that violations of policies, such as those which led to an investigation of the MACH trial, do not occur in any part of the agency. To this end, NIH initiated a variety of actions to address this issue, which will be discussed at the ACD meeting in December 2018, including:

- 1) Identifying issues of concern raised in the MACH trial and reviewing processes in support of public private partnerships and program development
- 2) Reviewing the training needs of NIH staff and developing case studies that describe appropriate program staff interactions with applicants
- 3) Developing additional questions for establishing public-private partnerships
- 4) Identifying basic considerations for the agency's risk analysis when evaluating potential public-private partnerships

NIH will continue to act swiftly and comprehensively if similar concerns arise in the future, as the integrity of the NIH grants administrative process, peer review, and the quality of NIH-supported research must always be above reproach.

⁵⁹ <https://www.nih.gov/news-events/news-releases/nih-end-funding-moderate-alcohol-cardiovascular-health-trial>.

⁶⁰ <https://acd.od.nih.gov/documents/presentations/06152018Tabak-B.pdf>.

⁶¹ <https://acd.od.nih.gov>.

- **Over the past several years, we have seen a number of troubling incidents at NIH that raise concerns about the agency's commitment to safe, unbiased research. The series of serious patient safety incidents at the NIH Clinical Center and the decision to shut down the \$100 million study into the effects of moderate drinking on cardiovascular health are just a few examples. This pattern of misconduct is unacceptable. What are you doing to protect against future misconduct and send a strong message – to NIH staff and all NIH- funded researchers – that safe, unbiased research is your agency's top priority?**

Answer:

NIH strives to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science, including a commitment to safe and unbiased research. A robust system of peer review and oversight and compliance by NIH staff and recipient institutions are all required to maintain the integrity of NIH-supported research. In response to recent events, the NIH has renewed its vigilance against inappropriate influences in our peer review process and funding decisions and has fortified our oversight of grantee responsibilities in reporting research misconduct and other types of inappropriate behavior in NIH-funded research.

The integrity of the NIH peer review process is critical for the agency to make informed funding decisions and for maintaining public trust in science. In response to recent events, NIH has re-examined and announced through Guide Notices (for example, NOT-OD-18-115)⁶², blogs,⁶³ and websites⁶⁴ the responsibilities of all participants in the NIH peer review process and consequences for a breach of review integrity (including confidentiality and/or security). In addition, Dr. Collins issued a statement⁶⁵ on protecting the integrity of U. S. biomedical research and sent a letter to 10,000 institutions that are grantees or NIH applicant organizations, asking for their assistance in identifying, reporting, and resolving inappropriate influences in NIH-funded research. A new Working Group of the Advisory Committee to the Director (ACD) is being assembled to assist, through the ACD, in advising Dr. Collins on Foreign Influences on Research Integrity.⁶⁶

In June 2018, an ACD Working Group for Review of the Moderate Alcohol and Cardiovascular Health Trial assisted the ACD in providing recommendations for the NIH to take steps to avoid inappropriate outside influences.⁶⁷ The NIH has undertaken a thorough examination of the roles and responsibilities of NIH Program Officials in developing and communicating program priorities and funding opportunities, managing a research portfolio, and communicating with applicants and grantees. Once completed, intensive training will be provided to Program Officials to clarify these issues and define standards of appropriate conduct and consequences for inappropriate conduct.

⁶² <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-115.html>.

⁶³ <https://nexus.od.nih.gov/all/2017/04/07/a-reminder-of-your-roles-as-applicants-and-reviewers-in-maintaining-the-confidentiality-of-peer-review>.

⁶⁴ https://grants.nih.gov/grants/peer/confidentiality_peer_review.htm.

⁶⁵ <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-protecting-integrity-us-biomedical-research>.

⁶⁶ <https://acd.od.nih.gov/working-groups/foreign-influences.html>.

⁶⁷ <https://acd.od.nih.gov/working-groups/machtrial.html>.

NIH is also taking steps to remind recipient institutions of their responsibilities in working with the NIH to protect human participants, live vertebrate animals, and the environment; to protect the scientific integrity of a project; and to ensure the proper expenditure of funds. A Guide Notice addressing these issues will be issued in early FY2019.

- **You recently sent a letter to research institutions regarding concerns with NIH-funded researchers failing to disclose financial contributions from foreign governments, diverting intellectual property overseas, and corrupting the peer review process. You have also established a working group including leaders from premier research institutions to examine how to address these issues moving forward.**
 - **What additional steps are you planning to communicate both with NIH employees and NIH-funded researchers to ensure they are in compliance with all laws and conflicts of interest requirements? What efforts will you be taking within NIH and broader research institutions to monitor compliance?**
 - **How are you communicating with HHS and other federal agencies regarding long-term strategies to ensure and protect the integrity of NIH-funded research?**

Answer:

NIH strives to ensure that the competitive process to award meritorious NIH biomedical research awards fair, transparent, and founded on integrity. In the August 2018 letter, NIH informed research institutions that some foreign entities have mounted systematic programs to influence NIH researchers and peer reviewers, thereby threatening the principles and policies surrounding NIH-supported research activities.

As a means to mitigate risks to research integrity while preserving and promoting the robustness of the biomedical research enterprise, NIH recently formed the ACD Working Group on Foreign Influences on Research Integrity.⁶⁸ This ACD working group, through the ACD, will help NIH to further support existing stringent policies guiding research. Specific charges to the working group include:

- Identify the best approaches for NIH and Universities, Research Institutions, and other Applicant Organizations, to partner to ensure that all sources of research support and all relevant affiliations and financial interests are accurately reported to the NIH
- Propose best approaches to facilitate appropriate collaboration with scientists across the globe, while helping to safeguard intellectual property in NIH applications or developed in whole, or in part, with support from the U.S. government
- Propose additional steps that NIH might employ to protect the integrity of the peer review process

⁶⁸ <https://acd.od.nih.gov/working-groups/foreign-influences.html>.

- Carry out these actions in a way that reflects the long tradition of partnership between NIH and grantee institutions, and that emphasizes the compelling value of ongoing honorable participation by foreign nationals in the American scientific enterprise

NIH is working and communicating with other government agencies, including appropriate security professionals and the broader biomedical research community, including NIH-funded institutions and U.S. university professional organizations, to identify steps that can help mitigate these unacceptable breaches of trust and confidentiality that undermine the integrity of U.S. biomedical research. The Director of the NIH Office of Policy for Extramural Research Administration, the chief grants management official for NIH, participates in the Executive Committee on Grants Administration Policy, which brings together senior grants managers from across HHS. NIH will use its participation in this forum to communicate NIH's efforts in this area and to facilitate discussion on strategies and opportunities for coordination to ensure and protect the integrity of research across the agency.

NIH reminded the extramural community in March 2018 that applicants and awardees must disclose all forms of other support and financial interests, including support coming from foreign governments or other foreign entities.⁶⁹ NIH expects institutions to work with their faculty and administrative staff to make sure that, in accordance with the NIH Grants Policy Statement,⁷⁰ all applications and progress reports include an accurate and complete account of all sources of research support, financial interests, and relevant affiliations. NIH expects that institutions notify the agency immediately upon identifying new information that affects an application or award. In addition, NIH continues to reach out directly to institutions when it becomes aware of potential issues involving compliance with policies on other support, financial conflict of interest, and peer review to request institutional reviews of the concerns. When issues of noncompliance are identified, NIH takes appropriate administrative action, which may include working with the recipient to identify a new principal investigator, notifying an investigator that their services in peer review are no longer needed, and coordinating with other government offices including the HHS Office of Inspector General. NIH fully expects that institutions will respond appropriately if any concerns arise related to the integrity of NIH-supported research.

NIH regularly communicates with grantees to provide training and compliance support for issues involving conflict of interest requirements, through NIH-led conferences such as the NIH Regional Seminar and professional organizations such as the Federal Demonstration Partnership, Society for Research Administrators and the National Council of University Research Administrators. In addition, NIH is currently developing an online training module on Financial Conflict of Interest that will serve as a resource for both NIH staff and the extramural community.

- **During the Committee's hearing on the implementation of the 21st Century Cures Act in December of 2017, we discussed the delay in appointing non-federal members to the Pregnant and Lactating Women (PRGLAC) Task Force. As you know, the 21st Century Cures Act required the Department of Health and Human Services to establish this Task Force 90 days after the law's enactment in**

⁶⁹ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-160.html>.

⁷⁰ <https://grants.nih.gov/policy/nihgps/index.htm>.

December of 2016. Given NIH's role in leading this Task Force, you assured the Committee that they should be fully participating members by the February 2018 meeting and that the Task Force should have recommendations later this year.

- **Were these nomination issues resolved before the February meeting of the Task Force?**
- **As the Task Force finalizes its recommendations, do you have a comment on NIH's commitment to working with Congress and other agencies to improve resources, guidance, and other information available to pregnant and lactating women?**

Answer:

The Task Force on Research Specific to Pregnant Women and Lactating Women ("Task Force" or "PRGLAC") was established by the 21st Century Cures Act (P.L. 114-255), and charged with providing advice and guidance to the Secretary of Health and Human Services (HHS) on activities related to identifying and addressing gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities. Appointed by the Secretary, the Task Force members' nominations were finalized prior to the February 2018 meeting. The Task Force was charged with preparing and submitting to the Secretary and Congress a report on its findings and recommendations by September 2018. In May 2018, the Task Force developed and voted upon 15 recommendations based on information gleaned during four open meetings and a public comment period. Throughout these discussions resonated the theme that cultural assumptions about use of medications by pregnant and lactating women need to be altered, which have significantly limited scientific knowledge of therapeutic product safety, effectiveness, and dosing for these groups of women.

Over six million women are pregnant in the United States each year. Of these women, more than 90 percent take at least one medication during pregnancy and lactation. However, pregnant women and lactating women are often excluded from clinical research that could ultimately help these populations. A comprehensive review of research in recent years conducted for the Task Force clearly showed the extremely limited information available on medication use in pregnancy and lactation. More evidence is needed so that women and their clinicians can make fully informed choices based on the risks and benefits of medicating or not medicating conditions during pregnancy and lactation. The provision of clinical data is essential to increasing the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women. Including pregnant and lactating women in clinical research – except when exclusion is scientifically justified – may require regulatory changes, targeted communications efforts with professional societies and the research community, and creative approaches to building a database of information about therapeutics that are already being used by pregnant and lactating women.

Per the 21st Century Cures Act, the charter of the Task Force will expire in March 2019. While NICHD/NIH currently supports research on medication use among pregnant women and lactating women with various medical conditions, including asthma, seizure

disorders, mental health disorders, and diabetes, we recognize that far more needs to be done to encourage inclusion of these populations in clinical studies, and plan to continue to work with other agencies represented on the Task Force to improve the evidence base for therapeutic decision making.

- **Many experts believe that immunotherapy is one of the most exciting fields in cancer research today, and I know it's one of the top priorities at the National Cancer Institute (NCI). Can you speak to us about the promise of immunotherapy, the importance of NCI research in this area, and how recent findings on tumor immunology and cancer immunotherapy could be applied to other diseases as well?**

Answer:

Scientists at the National Cancer Institute (NCI), as well as extramural researchers, are enthusiastic about the potential of immunotherapy, treatment that uses a patient's own immune system to help fight diseases. Based upon decades of basic immunology research supported by NCI and the National Institutes of Health (NIH), the recent successes in treating patients with few other therapeutic options has galvanized the research community to further explore this exciting field of study.

Currently, an important area of scientific focus is understanding why cancer immunotherapies work for some patients and not others. As part of the Cancer Moonshot™, NCI has established a new network of research centers and a data center with the goal of developing biomarkers for immunotherapy. Identifying biomarkers that can help predict which patients are likely to respond to immunotherapy will enable those patients to receive treatment sooner, while shedding light onto the mechanisms of resistance to immunotherapy. The network's four Cancer Immune Monitoring and Analysis Centers (CIMACs) will perform a range of molecular and cell-based testing on biospecimens—such as blood and tumor samples—from patients enrolled in early-phase immunotherapy clinical trials that are funded by NCI. These test results and clinical information about patients will be stored in the Cancer Immunologic Data Commons (CIDC), which researchers can then use in follow-up studies to identify potential biomarkers.⁷¹

Another Cancer Moonshot initiative is the creation of two networks to accelerate the translation of immunotherapy research discoveries to clinical applications for adult and pediatric cancers: the Immuno-Oncology Translational Network (IOTN) for adult cancers and the Pediatric Immunotherapy Discovery and Development Network (PI-DDN) for pediatric tumors. The aim of these networks is to develop and implement a national strategy to discover new immune targets and evaluate novel immune-based approaches, with the goal of increasing the cure rate in cancer patients and eventually to design vaccines to prevent cancers of all types. The IOTN will include a Cancer Immunotherapy Research Consortium, composed of Cancer Immunotherapy Research Projects⁷² and Cancer Immunoprevention Research Projects,⁷³ a Data Management and

⁷¹ www.cancer.gov/news-events/cancer-currents-blog/2018/immunotherapy-biomarkers-research-network.

⁷² www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-045.html.

⁷³ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-046.html.

Resource-Sharing Center (DMRC),⁷⁴ and a Cellular Immunotherapy Data Resource (CIDR).⁷⁵ The PI-DDN⁷⁶ will consist of PI-DDN Centers with comprehensive research programs that include both discovery and characterization of pediatric cancer immunotherapeutic targets and the identification of paths forward for the development of novel therapeutic strategies. Awards for both networks are expected by the end of fiscal year 2018.

In 2018, the NCI Center for Cancer Research (CCR), part of NCI's intramural program, launched the Center for Cell-based Therapy (CCT)⁷⁷ with the goal of facilitating the discovery and development of cellular immunotherapies, such as (chimeric antigen receptor) CAR T-cell therapy, an approach which was pioneered by NCI intramural investigators and approved by the Food and Drug Administration (FDA) in 2017. The CCT builds on NCI's decades-long efforts to understand the principles of cell-based therapies and to bring early stage research to the clinic. The CCT provides training for NCI staff and visiting investigators. This effort will spearhead the development of advanced treatment technologies with cell-based immunotherapy. Launched in 2017, the Cancer Moonshot-supported Partnership for Accelerating Cancer Therapies (PACT) is a collaboration between NCI and 11 pharmaceutical companies with the goal of rapidly expanding the immunotherapy therapies available to patients.⁷⁸ PACT's focus, with the benefit of guidance from the Food and Drug Administration (FDA), is to identify, develop, and validate robust biomarkers to advance new immunotherapies.

These efforts build upon the work of the Cancer Immunotherapy Trials Network (CITN), led by a cooperative agreement with the Fred Hutchinson Cancer Research Center. NCI established CITN in 2010 to design, facilitate, and conduct early-phase immunotherapy clinical trials and support research on patient tumor specimens.⁷⁹ The network currently has 30 participating trial sites and has conducted 10 clinical trials to date. CITN works with academic, industry, and nonprofit partners to advance promising immunotherapies to the clinic more efficiently and cost effectively.

The understanding of the immune system, based on decades of NCI and NIH-supported basic research, has built the foundation for immunotherapy approaches for cancer and for other diseases. For example, rituximab, an antibody that targets a certain protein on a type of immune cell called a B-cell, has been approved for B-cell non-Hodgkin's lymphoma, rheumatoid arthritis, and three other autoimmune diseases. The cancer therapy IL-2 (Aldesleukin), which stimulates the immune system to better attack cancer cells, is FDA approved to treat metastatic melanoma and renal cell carcinoma. Research is showing that in low doses, aldesleukin affects a type of immune cell called T regulatory cells, which suppress the unwanted immune responses that characterize autoimmune diseases. Therefore, aldesleukin is being investigated in patients for the treatment of autoimmune diseases,

⁷⁴ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-047.html.

⁷⁵ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-048.html.

⁷⁶ www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-004.html; <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-003.html>.

⁷⁷ www.ccr.cancer.gov/CenterForCellBasedTherapy.

⁷⁸ www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation.

⁷⁹ www.fredhutch.org/en/labs/science-projects/citn.html.

including type 1 diabetes⁸⁰, vasculitis⁸¹, lupus⁸², and ischemic heart disease.^{83,84} Similarly, anti-PD-1 and anti-PD-L1 checkpoint inhibitor therapies, which unleash the immune system to fight cancer, are being investigated as potential treatments for chronic viral infection, including hepatitis C virus and HIV.^{85,86,87,88} NCI will continue to collaborate with other NIH institutes and centers to identify how more patients can benefit from immunotherapy.

- **As you know, experts have grown increasingly concerned about the threat that antibiotic resistance poses to public health both domestically and internationally. In response to this threat, experts have developed a number of tools and initiatives to address the spectrum of issues tied to antibiotic resistance, ranging from applying antibiotic stewardship programs to a wide-range of clinical settings to CARB-X, a public-private partnership with BARDA, NIH, and other global partners to ensure a robust pipeline of preclinical innovation candidates that protect human health from the most serious bacterial threats.**
- **Almost 75 percent of antibiotics in clinical development are based on previously approved classes of antibiotics—novel structures and approaches are needed to stay ahead of resistance. While researchers are looking for out-of-the-box approaches to combat bacterial infections, such as using viruses to attack the bacteria, changing the gut microbiome to prevent infections, and modulating the human immune system to fight pathogens, many of these nontraditional approaches are in the preclinical stage and there is a clear need for studies that help bridge the divide between translational science and early-stage development.**
 - **How is NIH utilizing tools like CARB-X and the application of antibiotic stewardship programs in clinical settings to address the scientific barriers that hinder the discovery of new antibiotics?**
 - **What are the major scientific questions that NIH has pursued to study antibiotic resistance, including those pertaining to nontraditional approaches, as well as some of the promising results of that research so far?**

Answer:

The National Institute of Allergy and Infectious Diseases (NIAID) supports a comprehensive portfolio of research on the growing public health threat of antibiotic resistance. A critical goal of this research is to support the discovery and development of novel antibacterial products to diagnose, prevent, and effectively treat bacterial infections. NIAID has identified three main barriers to the discovery and development of new antibacterial therapies: 1) the scarcity of new antibacterial drug candidates effective against Gram-negative infections; 2) the challenge of

⁸⁰ www.clinicaltrials.gov/ct2/show/NCT03243058.

⁸¹ www.ncbi.nlm.nih.gov/pubmed/22129253.

⁸² www.ncbi.nlm.nih.gov/pubmed/27500725.

⁸³ www.clinicaltrials.gov/ct2/show/NCT03113773.

⁸⁴ www.ncbi.nlm.nih.gov/pmc/articles/PMC5837126.

⁸⁵ www.ncbi.nlm.nih.gov/pubmed/23717490.

⁸⁶ www.ncbi.nlm.nih.gov/pubmed/30232277.

⁸⁷ www.ncbi.nlm.nih.gov/pubmed/28431010.

⁸⁸ www.clinicaltrials.gov/ct2/show/NCT03239899.

enrolling patients in clinical trials needed to show efficacy of new therapeutics, especially in the case of Gram-negative drug-resistant infections; and 3) a lack of market incentives for pharmaceutical companies to invest in the final stages of antibiotic development and licensure.

NIAID provides targeted research support and services to offset challenges and de-risk antibacterial product development for researchers in industry and academia. These no-cost preclinical and clinical services include screening tests to identify compounds with antimicrobial activity and access to research reagents to evaluate promising product candidates. NIAID also supports CARB-X, a unique public-private partnership led by the Biomedical Advanced Research and Development Authority (BARDA). CARB-X is dedicated to accelerating the development of innovative antibacterial products from identification and characterization of therapeutic targets/candidates through Phase I clinical trials. CARB-X is currently supporting at least 28 therapeutic candidates, including ten new classes of antibiotics and 11 non-traditional agents, along with an additional five diagnostic products. Since the inception of the program, NIH has provided technical support and preclinical drug development services to more than half of CARB-X awardees.

NIAID also addresses these challenges in the development of new antibiotics by supporting early-stage development and facilitating clinical trials of new therapeutics. The NIAID-supported Antibacterial Resistance Leadership Group (ARLG) has developed a robust multisite clinical trials network that enrolled patients in over 35 clinical studies investigating new therapeutics, optimized treatment regimens, and diagnostic devices. The ARLG prioritizes research involving Gram-negative bacteria, which represent a major antimicrobial resistance threat, and is conducting a multi-site global observational clinical study to characterize the risk factors for and outcomes of infections caused by carbapenem-resistant Enterobacteriaceae (CRE). This also serves to enhance infrastructure for conducting future trials to address the challenge of CRE. NIAID enables antibiotic stewardship programs by supporting research to optimize existing antibiotics and develop novel, rapid diagnostics to distinguish between bacterial and viral infections, identify drug-resistant pathogens, and determine optimal treatment strategies at the point-of care. In addition, the NIAID ARLG is supporting the development of programs that include surveillance for resistant organisms, outbreak investigation, and clinical antibiotic stewardship programs. NIH also is partnering with BARDA on the Antimicrobial Resistance Diagnostic Challenge prize competition to identify innovative and rapid point-of-need diagnostic tests that will help inform appropriate antibiotic treatment.

NIAID-supported antibiotic resistance research is focused on key scientific questions, including how pathogens thwart host defenses and develop resistance to antibacterial drugs, in order to identify bacterial virulence factors and potential targets for novel diagnostics, vaccines, and therapeutics. NIAID also has solicited research for the development of tools to advance drug discovery of agents against Gram-negative pathogens and is facilitating scientific discussions and partnerships to address key questions and challenges in the development of new antibiotics. NIAID and The Pew Charitable Trusts sponsored the 2017 scientific workshop entitled, “Challenges in the Discovery of Gram-negative Antibacterials: The Entry & Efflux Problem” to help inform the identification and design of new types of antibiotics to help address the growing threat of resistant Gram-negative bacteria.

Success in addressing these key scientific questions about antimicrobial resistance is reflected by the number of promising products and approaches in the pipeline. NIAID estimates that more than 25 percent of the antibacterial candidates currently in clinical development previously received some form of NIAID support. For example, NIAID-supported scientists completed two Phase I clinical trials of a new class of antibiotics (CRS3123) for increasingly difficult to treat *Clostridium difficile* infections. NIAID also conducts and supports research on the development of innovative alternatives to antibiotics including bacteriophages, microbiome-based approaches, immune-based therapies, and vaccines. NIAID-supported scientists are working to identify protective commensal and symbiotic bacterial strains that could prevent and treat *C. difficile* infection. In addition, NIAID intramural investigators have identified a potential host-directed therapy using an antibody to boost the activity of neutrophils, a type of white blood cell, against carbapenem-resistant *Klebsiella pneumoniae*. NIAID also is supporting development of a novel vaccine candidate to prevent *Pseudomonas* infections; a new vaccine platform to provide broad protection against pathogenic *Shigella*, *Salmonella*, as well as *Pseudomonas*; and a novel immunoprophylactic against multidrug-resistant (MDR) Gram-negative pathogens.

NIAID recognizes the need for a concerted research effort to address key scientific questions and overcome technical challenges to combat the growing challenge of antibiotic resistance. NIAID continues to collaborate with academia, industry, and Federal partners to facilitate development of novel antimicrobial products, including non-traditional antibiotic approaches.

- **According to the Centers for Disease Control and Prevention, a record high of nearly 71,000 Americans died from drug overdoses in 2017. The country clearly needs new, innovative treatment solutions now. NIH has proposed using a coordinated strategy, working with the FDA and other stakeholders, to accelerate the development of new, non-addictive pain therapies to make a wide-range of therapeutics accessible to those who need them as quickly as possible.**
 - What types of non-addictive pain therapies are currently in the NIH research pipeline, and how quickly can these therapies be developed and distributed to the market to address this growing epidemic?
 - What process is NIH using to engage stakeholders in the community, such as small biopharmaceutical companies, so that all relevant stakeholders can play a role in shaping this important work?
 - Does NIH plan to consider vaccines as a potential public health solution to play a role in addressing the opioid use disorder crisis?

Answer:

The National Institute of Neurological Disorders and Stroke (NINDS), the lead institute at the National Institutes of Health (NIH) for pain research, and the other Institutes and Centers that make up the NIH Pain Consortium⁸⁹ are moving forward to meet the urgent needs of people with pain through a multi-pronged approach to develop safe and effective therapies that reduce our reliance on opioids. Three key areas of NIH's interest include: understanding the biological underpinnings of pain, accelerating discovery and development of non-addictive treatments, and rapidly advancing new treatments to the clinic.

⁸⁹www.painconsortium.nih.gov/.

NIH research to develop novel and non-addictive treatments for pain includes early-stage drug target discovery studies on molecular pathways of pain signaling, exploration of receptors and channels as potential non-addictive analgesic targets, and testing of novel treatments in preclinical behavioral models. For example, NINDS researchers identified nerve growth factor receptor and pain-related ion channels targets, which have led to industry-sponsored clinical trials for safe pain treatments for musculoskeletal pain and other pain disorders. NINDS supported early development of calcitonin gene receptor protein, the precursor to a compound recently approved to treat migraine. NIH programs for discovery of new formulations, combinations of medicines, and re-purposing molecules developed for other disorders are being expanded rapidly to find new pain medications. Through the NIH Blueprint Neurotherapeutics Program, which provides support for small molecule drug discovery and development, NINDS is funding research to develop a non-addictive treatment for headache and non-opioid analgesics for diabetic nerve pain.

NIH recently launched an exciting new initiative, the NIH Helping to End Addiction Long-term (HEAL) Initiative⁹⁰ which will enhance research to better treat addiction and opioid overdose, and to improve pain care, thereby reducing our reliance on opioids. HEAL supported projects will increase our understanding of pain, expand and expedite the development of non-addictive treatments, and rapidly advance new treatments to the clinic. As part of the HEAL Initiative, NIH is launching a large-scale clinical study to understand the mechanisms that lead to chronic pain after an acute injury. Data on many different biopsychosocial characteristics, such as gene variants, altered neural circuitry, inflammation, and mental health will be collected after an acute pain event and over the time during which chronic pain may develop. The data elements will be analyzed to provide a predictive signature to identify those at risk for chronic pain. This information will provide targets for novel drugs for acute pain treatment, guidance for precision medicine approaches to prevent chronic pain and reduce opioid use for those who are not likely to develop chronic pain.

Also through the HEAL initiative, NIH is partnering with academia and pharmaceutical companies to accelerate development of new pain medications. NIH has engaged many companies from both the analgesic drug and device development industry who will provide expertise, assets such as existing compounds which may have analgesic potential, and new compounds for development and testing through the HEAL infrastructure. As part of these efforts, NINDS and the National Center for Advancing Translational Sciences (NCATS) are leading a program to establish *in vitro* and *in vivo* platforms to accelerate discovery and testing of new non-addictive pain medications through rapid screening of molecules for analgesic relevant biological activity. Many NIH Institutes are collaborating to promote pain biomarker discovery and validation to inform early phase clinical testing of potential non-addictive therapies. To improve the chances of success in bringing medications to the clinic, NIH will facilitate the sharing of data on past and future drug development efforts across the biopharmaceutical industry and academia. To accelerate testing of novel pain treatments in humans, NINDS is establishing an Early Phase Pain Investigation Clinical Network that will speed the testing of new, non-addictive pain treatments through phase II clinical trials. The network will optimize trial design, target appropriate patients for trials,

⁹⁰ www.nih.gov/research-training/medical-research-initiatives/heal-initiative.

and engage experts in designing and performing clinical trials of promising pain treatments from industry and academia. A pain clinical trials research network to evaluate the effectiveness of novel treatments in later stage clinical trials also is being established to move therapies more rapidly into the clinic.

Another important part of the HEAL initiative includes a variety of efforts to treat opioid use disorder, including the development of a potential vaccine to induce long-lived antibodies capable of neutralizing opioids. The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute on Drug Abuse (NIDA) have partnered to establish a coordinated, multi-disciplinary consortium with the goal of developing opioid vaccines and testing them in clinical trials. The consortium will leverage NIAID's extensive vaccine development programs and resources, as well as NIDA investigators with expertise in opioid metabolism, biological transport, and mechanisms of action. To inform this effort, NIAID and NIDA will host a scientific meeting in the fall of 2018 focused on immunotherapies for the treatment of opioid use disorders.

- **Vaccines are one of the most effective and impactful public health successes in history. As Ranking Member of the Senate Labor, HHS, Education Appropriations Subcommittee, I was pleased to include report language along with the recent funding bill encouraging the National Institute on Aging to consider the development and testing of promising vaccine candidates for Alzheimer's disease a high priority. With the number of Americans diagnosed with Alzheimer's expected to rise to nearly 14 million by 2050, this language is particularly critical. Preliminary data on an anti-amyloid endobody vaccine for Alzheimer's shows an improvement or stabilization in certain cognitive conditions in its target sub-population.**
 - How has research supported by NIH thus far, or planned for the future, supported development of a vaccine, or combination therapies, to treat individuals with Alzheimer's?
 - Given the emergence of endobody vaccines that target non-infectious diseases, does NIH plan to expand extramural translation vaccine research efforts to support research on vaccines that can target neurodegenerative pathologies or pain mediators?

Answer:

Vaccination, a form of immunotherapy, is one of many treatment modalities currently under study for both the prevention and treatment of Alzheimer's disease (AD). 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 PET imaging who are at risk for developing dementia.

The National Institute on Aging (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.

Endobody vaccines, which “train” the body’s immune system to produce antibodies against undesirable proteins, have shown some promise against neurodegenerative disease in industry trials. They are similar in function to intracellular antibodies, or *intrabodies*, which are antibodies that work inside the cell to bind to potentially harmful proteins there. NIA supports a small portfolio of intrabody research, including preclinical development of an innovative gene therapy approach to deliver a dual intracellular/extracellular anti-tau antibody into the brains of individuals with Alzheimer’s disease. As we continue to expand our vaccine research program, we anticipate funding additional projects that harness intrabodies, as well as other novel approaches.

Although NIA does not currently support any projects on vaccines targeting pain mediators, the Institute, as part of the NIH’s Helping to End Addiction Long-term (HEAL) initiative, does participate in two recent Funding Opportunity Announcements (FOAs) to promote the discovery and validation of novel therapeutic targets to facilitate the development of non-addictive treatments for pain. Antibody-based treatments are included in this initiative. Projects funded under these FOAs will be active beginning in FY 2019.

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 FY 2019 and 2020.

- **As Ranking Member of the Senate Labor, HHS, Education Appropriations Subcommittee, I was proud to champion appropriations legislation that included \$429 million for the BRAIN Initiative—an increase of \$29 million—in addition to report language emphasizing the importance of big data. As you know, the Allen Institute in Washington State has made enormous contributions to the field of neuroscience and has been an important partner to the NIH in the early success of the BRAIN Initiative. It is my understanding the BRAIN Initiative Working Group 2.0 is seeking feedback on how to accomplish the vision described in the *BRAIN 2025: A Scientific Vision report*.**
 - **How will NIH utilize this feedback and increased support for the BRAIN Initiative to advance Big Science in which large, multi-disciplinary teams work together to generate and scale up innovative technologies to produce large, publicly available datasets?**

Answer:

The BRAIN 2025 report laid out an overarching vision that is as compelling now as it was when the NIH launched the BRAIN Initiative, with strong Congressional support. That report advised NIH that the Initiative must adapt its course in response to the rapidly evolving landscape of opportunities. The BRAIN 2.0 working group is reaching out extensively to the research community to assess progress and identify how the Initiative can best invest to realize its vision. Their report will guide NIH as the Initiative moves into its second half.

The Allen Institute's participation in the BRAIN Initiative illustrates how the BRAIN Initiative can successfully use community feedback to solicit proposals for pilot projects and then leverage results of those projects to develop and scale up innovative technologies to provide valuable data to the broader research community. One of the primary goals laid out in the BRAIN 2025 report is to identify and provide experimental access to all of the different brain cell types, which is essential to determine their roles in health and disease. In 2014, at its outset, the BRAIN Initiative funded ten teams, including researchers from the Allen Institute, to carry out pilot studies to develop innovative technologies to accomplish this goal. Building on the results from these pilot studies, in 2017 the Initiative funded multi-disciplinary teams spanning multiple institutions to form the larger scale BRAIN Initiative Cell Census Network, again including strong participation from the Allen Institute. As part of this consortium, the Initiative also funded a Brain Cell Data Center that is working with the network to establish web accessible datasets. This past year the BRAIN Initiative ramped up investment not only for the cell census, but also for other BRAIN Initiative goals to develop data archives, create data standards, and improve tools and methods for data integration and analysis. Across its major priorities, as for cell types, the BRAIN Initiative spurs innovation through smaller, pilot studies and scales up to larger team projects as appropriate to the status of the technologies, methods, and questions, with an emphasis on data sharing throughout.

Funding from the 21st Century Cures Bill has enabled the NIH to undertake large scale, ambitious projects such as the Cell Census Network and has also allowed NIH to successfully manage out-year commitments. For example, the BRAIN Initiative will be well positioned to respond to the guidance provided by the BRAIN 2.0 working group and to scale up "big data" resources as the early investments in technology bear fruit, thus providing data access and tools to take advantage of this information that are increasingly useful to the broader research community.

- **I was pleased to see NIH launch a Trans-NIH Pediatric Research Initiative to better coordinate and prioritize the pediatric research efforts across all institutes and centers. While the focus of the Initiative pertains to intramural research, the engagement of other stakeholders who are focused on children's health, such as academic institutions and children's hospitals, will be critical in shaping this important work.**
 - **What process will NIH use to engage the extramural research community that focuses on children's health in this Initiative?**
 - **How does NIH plan to incorporate the Initiative into larger efforts around developing a strategic plan for the Eunice Kennedy Shriver National Institute of Child Health and Human Development, particularly the component of the plan focused on child health activities?**

Answer:

The National Institutes of Health (NIH) funds more than \$4.4 billion in pediatric research annually; the majority of this funding is awarded to academic investigators across the country. To foster further coordination and collaboration among the NIH Institutes and Centers (ICs) that support pediatric research, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which supports about 18 percent of the overall NIH pediatric research portfolio, established the trans-NIH Pediatric Research Consortium (N-PeRC), representing each of the ICs, and several offices within the NIH Office of the Director. While ICs often work together on specific research issues (for example, Down syndrome, autism, and muscular dystrophy all have their own internal working groups), there has not been a trans-NIH mechanism to share information on pediatric research. Each IC has appointed a senior-level representative to the N-PeRC. The NIH Clinical Center is also represented, which will encourage coordination with our intramural scientists who are conducting pediatric clinical trials.

N-PeRC will allow NIH to take a more global view of NIH-supported pediatric research, bringing each IC's expertise to bear on a particular issue related to development or disease. A major goal of N-PeRC is to provide a collective voice on some of the health issues faced by children, and to help identify some of the highest priority areas for research, especially those that would benefit from collaboration.

The N-PeRC has met twice thus far and is committed to meeting every other month. Topics raised at the first meeting were possible coordination and collaboration on both extramural and intramural pediatric initiatives, consistent messaging across ICs about pediatric research needs, and increasing and maintaining the pediatric research pipeline. The N-PeRC is also reviewing each IC's pediatric research priorities to identify what might be needed to further these efforts. For example, early goals are to find additional ways to foster training for the next generation of pediatric clinician-researchers, and to conduct targeted outreach efforts to the extramural pediatric research community to increase representation on review panels. Another is to maximize the existing Best Pharmaceuticals for Children research program so that priority drugs can be tested for pediatric use.

As part of its future activities, N-PeRC will consider next steps toward an overall strategic vision for pediatric research at the NIH, which may include hearing about other agencies' activities in support of pediatric research and from external experts with expertise in particular aspects of pediatric research. In the meantime, NICHD is engaging in its own institute-wide strategic planning process; since just over half of NICHD's research is pediatric-focused, NICHD may be in an excellent position to extend the reach of both NICHD's and N-PeRC's priorities. In October 2018, NICHD held a milestone meeting in the plan's development to get input on NICHD's research priorities that included a broad range of pediatric experts from across the country.

Senator Robert P. Casey, Jr.

- **I understand that Ranking Member Murray is submitting a question about the recent National Academies of Science, Medicine, and Engineering report on the sexual harassment of women in science; I share her concerns and request that a copy of your response be provided to me as well.**

- **Dr. Collins, I appreciated the update in your written testimony about the work of the Beau Biden Cancer Moonshot initiative and the BRAIN Initiative.**
 - **What challenges do you still face in advancing research into cancer and neurological conditions and diseases, and how can we in Congress help you continue to drive this research forward?**

Answer:

Decades of investment in basic research and scientific inquiry have laid the foundation for the exciting scientific discoveries that led to the Cancer Moonshot™ and the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Led by the National Cancer Institute (NCI), and the National Institute of Neurological Diseases and Stroke (NINDS) and National Institute of Mental Health (NIMH), respectively, these initiatives represent cross-cutting, innovative platforms that have the potential to accelerate progress for patients. The scientific understanding of cancer is moving away from simply classifying a disease by the organ site in which it originated, and towards describing cancers by the genetic and molecular signatures of these diseases. Cancer may then be defined as a collection of hundreds, if not thousands, of distinct disease subtypes. The classification of these subtypes results in large datasets, often referred to as big data, that contain powerful information that, once analyzed, can illuminate future directions for therapy development.

This presents a complex, multidisciplinary challenge, as the cancer research community strives to effectively aggregate and analyze increasingly large and multifaceted data sets. Data is most useful when aggregated, as patterns in genetic or molecular alterations may only be apparent when a dataset contains a large number of entries, particularly for rare cancer subtypes. Therefore, NCI is deeply engaged in identifying and supporting new ways to combine data across studies and leverage these datasets. Recent big data initiatives include:

- The Genomic Data Commons (GDC)⁹¹ centralizes, standardizes, and makes accessible data from large-scale NCI programs to provide the cancer research community with a data service supporting the receipt, quality control, integration, storage, and redistribution of standardized cancer genomic data sets in support of precision medicine.
- The NCI Cloud Resources⁹² were initiated to explore cloud-based approaches for enhancing secure data access, collaboration, computational scalability, resource democratization, and reproducibility. Contracts awarded to the Broad Institute, the Institute for Systems Biology (ISB), and Seven Bridges Genomics in 2014 have supported development of the Cloud Pilots, which together provide infrastructure and a set of tools to access, explore, and analyze molecular data.
- Through the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C)⁹³, NCI has partnered with the Department of Energy to develop computational modeling tools to advance precision medicine oncology research. JDACS4C pilot projects include analysis of cellular, pre-clinical, and clinical data.

An important next step in leveraging big data for cancer research is combining genetic and

⁹¹ <https://gdc.cancer.gov>.

⁹² <https://cbit.cancer.gov/ncip/crdc-cloud-resources>.

⁹³ https://cbit.cancer.gov/ncip/hpc/jdacs4c_.

molecular data with clinical outcomes data. Combining these data will create new and incredibly valuable datasets, and also represents a powerful new resource that requires careful consideration of patient privacy and confidentiality. In 2018, NCI took an important step forward by establishing the National Clinical Trials Network/NCI Community Oncology Research Program (NCTN/NCORP) Data Archive, a centralized, controlled-access database that houses datasets generated from NCTN clinical trials. These datasets will be made available quickly, and with appropriate safeguards, to researchers for analysis of secondary studies to enhance the public health benefit of the original work. The archive serves to expand NCI's data sharing activities beyond genetic and genomic data into patient-level clinical trial data.

NCI will continue to build the framework for a national cancer research data ecosystem in which findings from basic research, translational studies, clinical trials, and more can be harmonized to lead to more rapid progress for patients.

NINDS faces similar challenges in managing big data to advance research against neurological disorders, particularly as the BRAIN Initiative scales up to generate more useful, multi-modal data. The BRAIN Initiative Cell Census Network, which is characterizing all the cell types in the brain, must bring together molecular, anatomical, physiological, connectivity, and other types of data for each cell type. NINDS is also investing in developing and validating biomarkers for neurological disorders, through multiple initiatives, including those focused on Parkinson's disease, chronic pain, rare diseases, and across all neurological disorders. Biomarkers will not only enhance NIH clinical research, but also remove a major obstacle to private sector investment, which is especially important because industry has been reluctant to take on the challenges of brain diseases. In addition to biomarker development, NINDS is improving the efficiency and effectiveness of clinical trials in other ways, for example by supporting development of outcome measures and other preparations for effective clinical trials as new therapies emerge for rare diseases and by development of clinical networks designed for early phase trials, for stroke, for emergency care interventions, and a forthcoming network to expedite the development of non-addictive pain interventions as part of the NIH Helping End Addiction Long-term (HEAL) Initiative.

Although NINDS works to optimize the management of research, the scientific and medical impediments to progress against neurological diseases present formidable barriers to progress. There are hundreds of different neurological diseases that arise from every type of cause imaginable—genes, trauma, infections, metabolic disorders, auto-immune attack, degenerative disease, and cancer, to name a few. The brain is also less accessible to and more perturbable by research and intervention than other organs—taking biopsy samples from the brain is usually precluded, and many potentially useful drugs are excluded by the “blood brain barrier.” Most importantly, scientists understand much less about how the brain works compared with organs like the kidneys, liver, heart, muscle, or lungs. When progress is not forthcoming against disease, a lack of understanding of how the brain normally works and what has gone wrong is often the obstacle.

NIH basic research ultimately drives progress in all disease areas, including neurological diseases and cancer, by both the public and private sector. For this reason, approximately half of the research supported by NIH is focused on basic science, including approximately seventy

percent of NINDS's budget and fifty percent of NCI's budget. While the Cancer Moonshot and BRAIN Initiative include many projects that aim to rapidly bring new treatments to patients, they will also continue to invest in the vital basic research that gives rise to future directions in therapeutic inquiry.

The research efforts described above, and the ability to meet the challenges of moving these and other complex initiatives forward, depend upon continued engagement and support from our Congressional colleagues.

Senator Tammy Baldwin

- **I am encouraged that the Pandemic and All-Hazards Preparedness and Advancing Innovation Act (PAHPAI) of 2018 includes language that I authored to direct BARDA to continue critical activities to prepare for threats like pandemic influenza.**
- **However, I remain extremely concerned that the measure does not include a separate, robust funding authorization for these efforts. Congress has failed to provide sustained and predictable funding for pandemic flu preparedness over the last decade. As a result, funding for the program has now been exhausted, leaving our pandemic flu stockpile full of expired vaccine components that don't match current strains.**
- **In a recent Op-Ed, the Assistant Secretary for Preparedness and Response, Dr. Robert Kadlec, urged Congress to authorize funding to prepare for an influenza pandemic. He wrote: "History is clear: the question is not if another influenza pandemic will occur but when and how severe it will be. Authorizing recurring funding to further improve our readiness for pandemic influenza is essential to achieving domestic preparedness."**
- **Do you agree that we should authorize funding for the pandemic influenza preparedness program and that it's not a matter of if we'll face another influenza pandemic, but when?**

Answer:

The National Institute of Allergy and Infectious Diseases (NIAID), the lead institute for research on infectious diseases at the National Institutes of Health, is supporting basic, translational, and clinical research on influenza that will improve our ability to prevent or respond to an outbreak of pandemic influenza. In order to prepare for the inevitability of a future influenza pandemic, NIAID supports the development of diagnostics, therapeutics, and vaccines effective against pandemic influenza strains, with the goal of eventual transition to the Biomedical Advanced Research and Development Authority (BARDA) for advanced development and potential inclusion in the national stockpiles.

The cornerstone of both seasonal and pandemic influenza prevention and control is the development of vaccines against influenza strains that may pose a significant risk to the public. NIAID currently is collaborating with BARDA to support development and evaluation of several candidate vaccines to protect against influenza strains with pandemic potential. In the last five years, the NIAID-supported Vaccine and Treatment Evaluation Units (VTEUs) have conducted ten clinical trials enrolling more than 3,000 volunteers to assess the safety and immunogenicity

of candidate pandemic influenza vaccines – including vaccines against the emerging H7N9 influenza virus – as well as adjuvants to boost the immune response of people receiving the vaccine. In addition, NIAID investigators are conducting clinical studies on vaccines for influenza strains with pandemic potential and collaborating with BARDA and industry partners to develop live, attenuated vaccines against these influenza strains.

To reduce the public health consequences of both seasonal and pandemic influenza, a broader, more durable “universal” vaccine is needed. NIAID recently published a strategic plan for universal influenza vaccine development to guide research investments in this area. A universal influenza vaccine has the potential to provide durable protection against multiple pandemic influenza strains and help eliminate the need for updating stockpiled vaccines in response to a change in circulating viral strains. NIAID is using funding for universal influenza vaccine research provided through the 2018 Consolidated Appropriations Act to continue to identify and evaluate novel universal influenza vaccine candidates, including a ferritin nanoparticle-based vaccine developed by the NIAID Vaccine Research Center and an experimental vaccine developed by NIAID scientists that uses non-infectious virus-like particles to elicit a protective immune response. In addition, the NIAID VTEUs are testing several universal influenza vaccine candidates, including M-001, a vaccine candidate that contains several influenza fragments that are recognized by the human immune system and are shared by multiple influenza strains.

NIAID is committed to supporting the basic, translational, and applied research necessary to develop a safe, effective, and durable universal influenza vaccine to protect against potential outbreaks of seasonal and pandemic influenza. NIAID continues to collaborate with BARDA to advance the development and clinical testing of promising influenza vaccine candidates.

Senator Elizabeth Warren

- **According to the American Foundation for the Blind, as our population ages, the risk of vision problems increases.¹ In FY18, NIH dedicated \$933 million across the agency to eye disease and disorders of vision.² However, according to the National Alliance for Eye and Vision Research, the annual cost of vision disorders in the U.S. is \$145 billion.³**
- **What avenues of research appear to hold significant promise in expanding our understanding of eye disease and vision disorder?**
- **How could research on eye disease and vision disorder expand our knowledge of non- vision-related biomedical challenges?**
- **How can NIH research support broader efforts to address vision disorders as our population ages?**
- **Does the NIH have ongoing partnerships with the Department of Defense or any other federal agency on vision research? If so, please describe these partnerships.**

• ¹ American Foundation for the Blind, “Special Report on Aging and Vision Loss,” Updated January 2013, <http://www.afb.org/info/blindness-statistics/adults/special-report-on-aging-and-vision-loss/235>.

• ² National Institutes of Health, “Estimates of Funding Various Research, Condition, and Disease Categories (RCDC),” May 18, 2018, https://report.nih.gov/categorical_spending.aspx.

• ³ National Alliance for Eye and Vision Research, “The vision community urges FY2019 NIH funding of at

least

- \$39.3 billion and NEI funding of at least \$800 million,”
<http://www.everresearch.org/pdf/FY2019NIHNEIFundingPosition.pdf>.

Answer:

Vision research is on the cutting-edge of developing tomorrow’s biomedical therapies and technologies such as gene therapy, regenerative medicine, functional imaging, and neuroplasticity. Features unique to the eye enable pioneering research that cannot be done in other parts of the body. Unlike our internal organs, the eye is both accessible and transparent, allowing researchers to easily treat the eye with lasers or injections, or to use non-invasive tools to image retinal neurons at the cellular level in patients. The retina, like the brain, is part of the central nervous system. Retinal neural circuits that convert visual images into signals transmitted to the brain are exceedingly complex, but vision researchers have made great progress decoding their mysteries, which is the first step in understanding the brain. In fact, nearly 40 percent of the projects funded in the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative either involve vision directly or include researchers with prior funding from the National Eye Institute (NEI) on their investigative team. Research on rehabilitation for low vision or blind individuals has demonstrated the power of brain plasticity—the ability of neurons to adapt and remodel their circuits—helping researchers design therapies to maximize remaining vision, or help individuals navigate, engage with prosthetic or assistive devices, and live independently.

Regenerative medicine is a new field that uses stem cells to regrow tissues that have been damaged. The NEI Audacious Goals Initiative (AGI), launched in 2013, is a 15-year effort to restore vision through regeneration of neurons and connections in the eye and visual system. The initiative funds collaborative research consortia, which are each approaching this complicated challenge from different angles. The impact of AGI will benefit other neurodegenerative diseases like Parkinson’s and Alzheimer’s Disease. NEI scientists are also about to launch a stem cell therapy to treat dry age-related macular degeneration (AMD), a leading cause of blindness, for which there is currently no cure. In this trial, researchers use AMD patient-derived stem cells to create and later transplant an important tissue in the retina called the pigment epithelium. In 2017, NEI launched the 3D Retinal Organoid Challenge, a \$1.1 million prize competition to develop methods to use stem cells to generate miniature retinas in a lab dish, which can be used for disease modelling and drug development.

The eye also has unique immune properties, such as relative immune privilege, enabling corneal transplants without rejection by the immune system or the need for immunosuppressive drugs. Furthermore, with two eyes, clinical trials can test a therapy in one eye, while leaving the other as an internal control for comparison in the same patient. Hence, the eye is the target of choice for pioneering gene therapy research, a pipeline that includes at least 20 current clinical trials. In 2017, the FDA approved the first gene therapy in the eye for a rare form of childhood blindness called Leber Congenital Amaurosis. The field of ocular genetics has discovered hundreds of genes in humans that, when mutated, can lead to vision loss. Using a few cells removed from patients with genetic eye disease, scientists can create stem cell lines to study the disease in the lab. They can also correct the mutation in these cells using a paradigm-shifting gene editing tool known as CRISPR, which may form the basis for a future cell therapy.

NIH has been establishing research partnerships with other Federal agencies. For example, the Collaborative Research in Computational Neuroscience is a partnership between NIH and the National Science Foundation as well as international funding agencies. The program promotes collaborative science and engineering projects through a common grant application process that expedites review across agencies—matching projects with the most appropriate funding agency. Similarly, NEI is developing a program with the vision research program at the Department of Defense (DoD). The DoD receives many more applications relating to traumatic eye injury, burns, and battle injuries than it can fund; by aligning review criteria, NEI and DoD will be able to jointly review qualified projects that fit within their research missions.

Senator Tim Kaine

- **Chairman Alexander, Ranking Member Murray and the members of this Committee are working towards passing a comprehensive opioids package. This crisis, along with substance use disorder generally, continues to devastate communities in Virginia. Drug overdoses killed about 72,000 Americans last year, a record number that reflects a rise of around 10 percent, according to recently released preliminary estimates from the Centers for Disease Control.**
- **When you came before HELP last year, I asked about the possibility of reaching a goal of being “Addiction Free” by 2030. How can we help move towards that goal? Can you also provide an update on the Health to End Addiction Long-term (HEAL) Initiative that was launched in April?**

Answer:

Ending addiction requires that effective, evidence-driven prevention and treatment interventions be efficiently delivered to populations who need them. Toward this goal, NIH is both developing and testing those interventions, and studying their implementation into real-world settings, including school, workplace and community settings and within the health care system, in emergency departments, primary care settings, and beyond.

NIH has planned an audacious research program with the goal of ending addiction—the Helping to End Addiction Long-term (HEAL) Initiative, which was launched in April 2018. HEAL will support research across NIH, using \$500 million of Fiscal Year 2018 funds appropriated by Congress, to improve treatments for opioid use disorder and addiction, and enhance pain management. Using these funds, NIH has planned the following studies which aim to advance us towards the goal of ending addiction:

- New research grants to study the impact of behavioral interventions for the prevention of Opioid Use Disorder (OUD).
- Expansion of the size and scope of research conducted by the National Drug Abuse Treatment Clinical Trials Network, incorporating new research sites and investigators into existing research nodes and centers, adding opioid-related research into studies currently underway, expediting new studies in general medical and other settings, and enhancing clinical and research training opportunities.
- The Justice Community Opioid Innovation Network, which will establish a network of research investigators to rapidly conduct studies on quality care for opioid misuse and OUD in justice populations by facilitating partnerships between local and state justice systems and community-based treatment providers.

- Funding opportunities to develop new treatment strategies for OUD, including new or stronger, longer-lasting formulations of existing medications; novel medications; immunotherapies; and devices to treat withdrawal, craving, progression, and relapse.
- The HEALing Communities study, in collaboration with SAMHSA, will test the integration of prevention, overdose treatment, and medication-assisted treatment in an array of settings in communities that are highly affected by the opioid crisis. This research will help define community prevention and treatment models that are most likely to reduce addiction and overdose deaths in communities nationwide. Both through the NIH-wide HEAL Initiative and the continuing efforts of the National Institute on Drug Abuse, NIH is pursuing progress towards the goal of reducing the burden of addiction and substance use, and sustainably incorporating prevention and treatment into the healthcare system to create lasting impacts on public health.

Senator Tina Smith

- **I'm proud of the bipartisan opioids package we passed out of the HELP Committee, because I think it will provide real relief to families and communities in Minnesota. But we're also facing a broader crisis—in Minnesota, meth use is on the rise in many communities and as the CDC highlighted in June, suicide rates are going up. Taken together, public health officials in my state talk about these challenges as 'diseases of despair.'**
- **Has NIH identified connections between these behavioral issues—like addiction and suicide—that could inform our work in Congress to support affected communities?**
- **And has NIH identified any best practices to address the broader collection of diseases of despair? And how can we build resilient systems and infrastructure to support communities in developing strategies that address diseases of despair?**

Answer:

The National Institutes of Health (NIH) recognizes the challenges associated with these “diseases of despair” and the misfortunes they bring to communities across this country. To address these public health concerns, NIH supports research on substance use disorders, mental illnesses, connections between the two, and research on the tragic outcomes when they are left untreated, including suicide. NIH funds a range of research, from basic research to understand the causes of substance use and mental health disorders, including neural mechanisms, genetics underpinnings, and environmental risk factors, to clinical research that may lead to improved prevention and treatment.

Comorbidity of substance use disorders and mental illnesses is, unfortunately, common. According to the Substance Abuse and Mental Health Services Administration (SAMHSA), in 2017, 8.5 million adults in the United States had both a mental illness and a substance use disorder in the past year, which corresponds to 3.4 percent of adults.⁹⁴ The circuits in the brain that mediate reward, stress, decision making, impulse control, and emotions may be affected by

⁹⁴ SAMHSA. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Retrieved from <https://www.samhsa.gov>

addictive substances and disrupted in substance use disorders, as well as in depression, schizophrenia, and other mental illnesses. Research also suggests there are many genes that may contribute to the risk for both mental disorders and addiction, including genes that influence the action of neurotransmitters—chemicals that carry messages from one neuron to another—which are affected by drugs and commonly dysregulated in mental illnesses, such as dopamine and serotonin. Environmental factors such as chronic stress, trauma, or drug exposure can induce changes in gene expression, which can alter functioning in neural circuits and ultimately impact behavior. NIH invests in research to understand the intertwined nature of both causes and symptoms of comorbid substance use disorders and mental illnesses, as well as research incorporating that understanding into effective treatments.

Unfortunately, SAMHSA also reports that approximately half of U.S. counties lack even one practicing mental/behavioral health specialty clinician.⁹⁵ Given the public health urgency and need for services to address “diseases of despair,” NIH is funding new research that aims to develop and implement pragmatic, effective, scalable, and sustainable solutions that could allow the healthcare system to cope with pressing behavioral/mental health needs. For example, as part of the HEAL (Helping to End Addiction Long-term) Initiative, the NIH will support research to identify service delivery models for treating mental/behavioral health conditions to meet the needs of individuals with opioid use disorders and co-occurring mental illnesses. NIH also remains committed to reducing the rising rate of suicide in this country. Specifically, the National Institute of Mental Health (NIMH) is funding research to identify at-risk individuals, develop treatments, improve quality of life, and prevent suicide deaths. For immediate impact, researchers are examining the best ways to effectively implement evidence-based practices into healthcare systems and communities. Over the longer-term, NIMH-funded scientists are laying the groundwork for the transformative treatments of tomorrow through careful basic science.

Moving forward, NIH will continue to support research on prevention, treatment, and services to inform the work of other federal agencies in their efforts to provide evidence-based treatment and service delivery. NIH remains a committed partner with others in the federal government, the private sector, and local communities as they build resilient systems and strategic infrastructure to address “diseases of despair.”

Senator Doug Jones

- **By most accounts, the United States holds the worst infant mortality record in the developed world. In Alabama, our infant mortality rate is particularly troubling – in 2017, roughly 9 out of 1,000 infants died before celebrating their first birthday. This rate is higher than Bahrain, Sri Lanka, Costa Rica, and many other developing countries. Evidence has shown that racial disparities in maternal and infant health outcomes are driving this infant mortality crisis. Dr. Collins, what is the NIH doing to better understand the causes of these disparities? What steps have been taken at the NIH and what can Congress do to address infant mortality?**

Answer:

⁹⁵ SAMHSA. (2013). *Report to Congress on the Nation's Substance Abuse and Mental Health Workforce Issues* (Publication ID: PEP13-RTC-BHWORK). Retrieved from <https://www.samhsa.gov>.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) continues to actively support a large and diverse research portfolio related to the causes and prevention of infant mortality, as well as determinants of healthy pregnancies. Preterm birth infants, or those born before 37 weeks of gestation, suffer from significantly increased risk for neonatal mortality, and long-term pulmonary and neurodevelopmental morbidities. According to the Centers for Disease Control and Prevention, in 2016 preterm birth affected about one in 10 infants born in the United States, but with a 50 percent higher incidence for African-American infants.

Among the NICHD's research priorities are developing specific predictive algorithms that include physiological, biochemical, and genetic markers to predict pregnant women at risk for pregnancy loss and/or stillbirth (as well as women whose infants may be at risk of sudden infant death syndrome, SIDS). Other priorities include discovery of physiological and molecular mechanisms involved in normal and abnormal formation of the placenta and other early factors in establishing healthy pregnancy. The NICHD Maternal and Fetal Medicine Units Network (MFMU) focuses on clinical trials with a goal of reducing maternal complications of pregnancy as well as fetal and infant mortality and morbidity. Having the ability to enroll large populations of pregnant women in MFMU-supported clinical trials is critical in helping to decipher the factors involved in preterm birth. For example, an ongoing MFMU clinical trial is testing whether the use of cervical pessary in women with a short cervical length will reduce the risk for preterm birth in singleton pregnancies. Another NICHD-funded network, the Global Network, is supporting a range of clinical trials in resource-poor settings to find low-cost, sustainable interventions to improve maternal and child health. For example, in collaboration with the World Health Organization, one trial is testing whether providing antenatal corticosteroids can increase neonatal survival in developing countries.

Several other NICHD-funded studies are aimed at the prevention of preterm births. One study showed that overweight or obese pregnant women, who had no history of chronic disease before pregnancy, were at significant risk of preterm birth compared to normal weight women. Another study of 10,000 nulliparous women (women who had never before given birth), co-funded by the NICHD and the National Heart, Lung, and Blood Institute, showed that sustained low leisure-time physical activity across pregnancy is associated with excess risk of gestational diabetes and overall preterm birth compared to higher patterns of activity. These findings raise the possibility that increases in activity early during pregnancy may be associated with improved pregnancy health. A NICHD-supported randomized controlled trial found that intraventricular hemorrhage (bleeding in the brain), which occurs more frequently in preterm births, could be prevented or ameliorated by delayed umbilical cord clamping, alone or in combination with an approved medical therapy.

The NICHD is funding multiple initiatives to better diagnose and understand birth outcomes. The 'Human Placenta Project' (HPP) aims to better understand the placenta, arguably the least understood human organ and one that greatly influences the health of a woman and fetus during pregnancy. One goal of the HPP is to identify non-invasive markers for prediction of adverse pregnancy outcomes including preterm birth. The NICHD's newly launched PregSource® project uses a crowd-sourcing approach to learning about typical pregnancies, asking pregnant women who wish to participate to enter information regularly throughout gestation and the early

infancy of their babies, into online surveys and trackers via a website. A large resource library that includes evidence-based information about pregnancy management, issues, and complications is available to participants.

- **As you know, the maternal mortality rate in the United States is on the rise. Like infant mortality, racial and geographic disparities in maternal health are of particular concern. I am proud to have cosponsored S. 1112, the Maternal Health Accountability Act of 2017, introduced by Senators Heitkamp and Capito, which seeks to expand the maternal mortality review committees (MMRCs) that study and address the causes of maternal death cases in most states. What is the NIH doing to understand why maternal mortality is on the rise and to identify solutions to address this crisis? How would improving state-level reporting and data on maternal deaths affect NIH research on this issue?**

Answer:

The prevalence and potential severity of pregnancy complications, for women as well as the fetus and newborn, make research to inform better treatment and prevention a high priority. Along with other NIH Institutes, Centers, and offices, NICHD supports a wide range of investigator-initiated grants. In addition, NICHD's longstanding Maternal-Fetal Medicine Unit Network (MFMU) designs and evaluates research studies on maternal health and reducing complications of pregnancy; evidence from Network studies has resulted in many clinical guidelines promulgated by professional societies. Recently, for example, similarities in pathological characteristics of cardiovascular disease and preeclampsia, a dangerous spike in a pregnant woman's blood pressure, prompted NICHD-supported researchers at the MFMU to conduct a preliminary study of a commonly used cardiovascular drug (Pravastatin) in high risk pregnant women. Women receiving this drug in the second trimester of pregnancy did not develop preeclampsia, while those receiving the placebo did develop this serious pregnancy complication at the same rate as pregnant women in the general population.

NICHD's Obstetric-Fetal Pharmacology Research Network tests therapeutics taken by women during their pregnancies. Some of this work informed the congressionally mandated Task Force on Research Specific to Pregnant Women and Lactating Women, which just submitted a report with recommendations about how to include these populations in research. The intramural Perinatology Research Branch conducts studies on high-risk pregnancies, with attention to both maternal and infant health outcomes; what we learn from high-risk pregnancies in the United States can be applied to our work globally. NICHD's Global Network for Women's and Children's Health Research focuses on widespread issues such as preventing postpartum hemorrhage, improving childbirth practices, and reducing infections in low-resource settings. Collection of accurate data on maternal mortality has long been a priority for NICHD. Without better data collection and review, researchers will not be able to accurately determine the reasons women die from pregnancy complications. Better data would allow NIH-supported investigators to analyze the associations and trends in maternal exposures, and pinpoint possible areas for interventions. The Population Dynamics Branch funds research to gather information and statistics on maternal mortality and analyze those data, and just in the past month, NICHD entered into an agreement to fund additional questions for CDC's Pregnancy Risk Assessment Monitoring System (PRAMS) to look at the influence of disability on pregnancy risks and

maternal and infant outcomes.

In addition, NICHD recently entered into a major contract with the National Academy of Sciences for a consensus study on the choice of birth settings and maternal and infant outcomes. Among the issues to be considered by the independent panel are the social determinants that influence risk and outcomes in various birth settings, financing models for childbirth across birth settings, and training issues for health care professionals. The panel's report is expected in early 2020.

- **A number of colleges and universities, including many Minority-Serving Institutions (MSIs), have expressed concerns about proposed changes to diversity programs including the Maximizing Access to Research Careers (MARC) and Research Initiative for Scientific Enhancement (RISE) programs at the National Institute of General Medical Sciences. Specifically, there is tremendous concern within the community that proposed changes may reduce support for research active institutions serving large concentrations of the most at-risk students. Would you please explain these proposed changes and respond for the record as to their purpose, how the distribution of diversity grants to institutions of higher education will be affected, and the likely effect on underserved students?**

Answer:

The National Institute of General Medical Sciences (NIGMS) has a longstanding commitment to developing a diverse pool of biomedical scientists through a variety of institutional training and student development programs. The NIGMS is committed to continuing its support of trainees at a range of institutions, including individuals at Minority Serving Institutions (MSIs). In Fiscal Year 2018, the Division of Training, Workforce Development and Diversity (TWD) at NIGMS provided funds for awards at 97 Minority Serving Institutions, including 25 Historically Black Colleges and Universities (HBCUs), 3 Predominantly Black Institutions (PBIs), 1 Tribal College and University (TCU), 25 Asian American and Native American Pacific Islander-Serving Institutions (AANAPISIs), 10 American Indian Alaska Native Serving Institutions (AIANSIs), and 33 Hispanic-Serving Institutions (HSIs). The adjustments to the diversity enhancing programs described below are not intended to change the distribution of institutions NIGMS supports. The NIGMS has not changed its longstanding commitment to funding meritorious applications from Minority Serving Institutions and will continue to conduct outreach to them to ensure that students at these institutions have access to robust biomedical training experiences. The NIGMS does not anticipate any significant change to the distribution of institution types that it supports and will continue to actively monitor the institutions represented within its TWD portfolio. As described below, the adjustments that the Institute is making to its diversity enhancing programs are designed to improve NIGMS' ability to support outstanding research training at research-active institutions, including MSIs, and should significantly benefit the students these institutions serve.

Based on stakeholder feedback obtained through Requests for Information ^{96, 97}), as well as extensive analyses and discussions with NIH staff and the extramural scientific community, the NIGMS is in the process of making adjustments to its programs in order to further promote and enhance the diversity of the biomedical research workforce. The adjustments, which have recently been approved by the NIGMS Scientific Advisory Council, are fully consistent with the GAO's 2017 and 2018 recommendations regarding: a) the use of program evaluations and stakeholder input to improve the efficiency and effectiveness of government resources⁹⁸, and b) the reduction of duplication and overlap in the design and implementation of STEM education programs⁹⁹). The adjustments described below are thus designed to: 1) provide enhanced equity of trainee support across programs; 2) minimize or prevent programmatic overlap; 3) align funding strategies with programmatic goals; 4) tailor expectation of outcomes, support mechanisms, and review considerations to an institution's level of research activity; and 5) strengthen NIGMS' ability to evaluate the success of these programs. The changes, described in more detail in the recent Videocast of the May, 2018 NIGMS Advisory Council Open Session (starting at 1:43:26)¹⁰⁰ and Videocast of the September Council Open Session (starting at 1:07:22)¹⁰¹, involve the Initiative for Maximizing Student Development (IMSD)¹⁰², the Research Initiative for Scientific Enhancement (RISE)¹⁰³, the Maximizing Access to Research Careers - Undergraduate Student Training in Academic Research (MARC U-STAR)¹⁰⁴, as well as the Bridges to the Baccalaureate¹⁰⁵ and Bridges to the Doctorate¹⁰⁶ programs. The NIGMS does not anticipate any immediate changes to the Postbaccalaureate Research Education Program (PREP)¹⁰⁷.

Specifically, the modifications are intended to accomplish the following aims:

- Better align the programmatic goal of preparing trainees for careers that have a significant impact on the health-related research needs of the Nation with the funding approach used to support this goal. The NIGMS plans to accomplish this aim by transitioning from the Research Education (R25) activity code to the National Research Service Award (NRSA) Training (T) mechanisms.
- Provide more equity across NIGMS programs for trainee stipends and tuition remission. The switch from the R25 activity code to T mechanisms described above will benefit

⁹⁶ Request for Information on NIGMS Programs to Enhance Diversity in the Biomedical Research Workforce, NOT-GM-15-108, February 24, 2015.

⁹⁷ Notice Request for Information: Organization and Administration of NIGMS Undergraduate and Pre-Doctoral Diversity Programs, NOG-GM-17-107, August 31, 2017.

⁹⁸ GAO Program Evaluation: Annual Agency-Wide Plans Could Enhance Leadership Support for Program Evaluations, GAO-17-743, September 2017.

⁹⁹ GAO 2018 Annual Report: Additional Opportunities to Reduce Fragmentation, Overlap, and Duplication and Achieve Other Financial Benefits, GAO-18-371SP, April 2018.

¹⁰⁰ Videocast, NIGMS Advisory Council Open Session, <https://videocast.nih.gov/summary.asp?Live=27879&bhcp=1>.

¹⁰¹ Videocast, September Council Open Session, <https://videocast.nih.gov/summary.asp?live=28435&bhcp=1>.

¹⁰² Initiative for Maximizing Student Development: <https://www.nigms.nih.gov/Training/IMSD/Pages/default.aspx>.

¹⁰³ Research Initiative for Scientific Enhancement: <https://www.nigms.nih.gov/Training/RISE/Pages/default.aspx>.

¹⁰⁴ Maximizing Access to Research Careers - Undergraduate Student Training in Academic Research:

<https://www.nigms.nih.gov/Training/MARC/Pages/USTARAwards.aspx>.

¹⁰⁵ Bridges to the Baccalaureate:

<https://www.nigms.nih.gov/Research/Mechanisms/Pages/BridgesBaccalaureate.aspx>.

¹⁰⁶ Bridges to the Doctorate: <https://www.nigms.nih.gov/Research/Mechanisms/Pages/BridgesDoctoral.aspx>.

¹⁰⁷ Postbaccalaureate Research Education Program: <https://www.nigms.nih.gov/Training/PREP/Pages/default.aspx>.

student trainees supported by the Institute by ensuring they receive stipends as well as tuition remission to advance their scientific career goals and reduce or eliminate any debt they might have incurred for their education.

- Create separate institutional eligibility tracks for review and funding based on NIH research project grant funding levels. The two tracks include a research-intensive track, i.e., for institutions with a 3-year average of NIH research project grant (RPG) funding greater than or equal to \$7.5 million, and a research-active track, i.e., for institutions with a 3-year average of RPG funding less than \$7.5 million (RPG data are available through NIH RePORTER). By separating these two tracks of institutions, NIGMS will be able to ensure that each is compared to others of a similar type during the peer review process, which will benefit the research-active institutions because they will not have to compete for funding with universities that already have much higher levels of research infrastructure and support. In addition, NIGMS will be able to monitor and manage the levels of funding for each class of institution to ensure that resources do not inappropriately accumulate at the better-funded schools at the expense of the less well-funded ones.
- Convert the Bridges to the Baccalaureate program to the T34 activity code and encourage programs to provide enriching activities before and after the bridge.
- Continue the MARC (NOT-GM-18-031¹⁰⁸) program to support the training of research-oriented undergraduates at research-intensive institutions.
- Convert the current RISE research education program into two separate training programs: one to support the training of undergraduates called the Undergraduate Research Initiative for Student Enhancement, or U-RISE (NOT-GM-18-030¹⁰⁹), and the other to support predoctoral training called the Graduate Research Initiative for Student Enhancement, or G-RISE (NOT-GM-18-029¹¹⁰). RISE masters' programs are encouraged to apply for the NIGMS Bridges to the Doctorate Program. RISE programs are intended for research-active institutions.
- Convert the Bridges to the Doctorate to the T32 activity code and remove the cap placed on the size of the program to accommodate master's-level RISE programs that will transition into the Bridges to the Doctorate program.
- Convert the current IMSD research education program into an IMSD (NOT-GM-18-028¹¹¹) training program that supports predoctoral training at research-intensive institutions. IMSD programs that currently support undergraduates are encouraged to apply for the MARC or U-RISE program, depending on institutional eligibility.
- Minimize the duplication of diversity-focused NIGMS programs. Each institution will be eligible for one diversity-focused undergraduate program (either MARC or U-RISE) and one diversity-focused graduate program (either IMSD or G-RISE).

¹⁰⁸ Notice of Intent to Publish a Funding Opportunity Announcement for the Maximizing Access to Research Careers (MARC) (T34) Program, NOT-GM-18-031, May 30, 2018.

¹⁰⁹ Notice of Intent to Publish a Funding Opportunity Announcement for the Undergraduate Research Initiative for Student Enhancement (U-RISE) (T-34) Program, NOT-GM-18-030, May 30, 2018.

¹¹⁰ Notice of Intent to Publish a Funding Opportunity Announcement for the Graduate Research Initiative for Student Enhancement (G-RISE) (T32) Program, NOT-GM-18-029, May 30, 2018.

¹¹¹ Notice of Intent to Publish a Funding Opportunity Announcement for the Initiative for Maximizing Student Development (IMSD) (T32) Program, NOT-GM-18-028, May 30, 2018.

- Tailor programs and review considerations to the specific strengths and needs of research-active and research-intensive institutions and their students. This tailoring will help ensure that NIGMS' funding strategies optimally support each type of institution and its students.
- Enhance the capacity for NIGMS to monitor and evaluate programmatic outcomes.

The Funding Opportunity Announcements (FOAs) for these programs to enhance diversity in the biomedical research workforce will encourage applications from training programs that do the following: focus on skills development (including an emphasis on quantitative and computational skills); promote rigor and reproducibility in research; teach the responsible and safe conduct of research; encourage inclusive, safe, and supportive research environments; use evidence-based, innovative educational and mentoring practices; employ cohort-building activities and interventions that enhance the trainees' science identity and self-efficacy; provide individualized mentoring and oversight throughout the trainees' undergraduate or graduate careers; and introduce trainees to a variety of scientific research areas and career trajectories.

For institutions with currently funded IMSD, RISE, and MARC programs, the policies and guidance in the FOAs under which the current programs were funded will be applicable until the end of the current funding cycle. The NIGMS intends to release the MARC, U-RISE, IMSD, and G-RISE funding announcements in the fall of 2018 and the Bridges to the Baccalaureate and Bridges to the Doctorate programs early in 2019. All applications for these programs must be submitted under the new FOAs. The NIGMS will conduct extensive outreach to provide guidance while institutions and existing programs navigate this transition.

[Whereupon, at 11:28 a.m., the hearing was adjourned.]

