DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2020

THURSDAY, APRIL 11, 2019

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

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

Present: Senators Blunt, Shelby, Alexander, Moran, Capito, Lankford, Murray, Durbin, Shaheen, and Baldwin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

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

ACCOMPANIED BY:

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

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

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

JON LORSCH, PH.D., DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

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

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

OPENING STATEMENT OF SENATOR ROY BLUNT

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

This is always a good hearing for us. I think, in the 4 years that Senator Murray and I have worked on this committee together, we clearly have made NIH one of our priorities, and we're glad it has been.

We have increased funding by $9 billion, a 30 percent increase over 4 years, and hopefully we are not done with that process yet, but hearing what you are doing with that money always helps encourage us to not only make those dollars available, but even more.

We have seen real progress in vaccine research from Ebola to Zika, we have seen the development of blood tests to detect different kinds of cancer earlier than had been before, the first-ever drug used specifically for postpartum depression has been developed during this period of time. Obviously, what is happening in immunotherapy, which at our first hearing was something that had to be explained to all of us and even a few of your colleagues, as it was developing in the amazing way it has already.

I think we have seen ways that you have found to encourage young researchers and hopefully we will be able to hear a little more about that today, as well.

In my home State of Missouri, research has demonstrated that interactive therapy can reduce rates of childhood depression, a discovery of an enzyme responsible for the spread of cancer, and we have seen research supported that aimed at improving the scaling-up of immunotherapy and how to make that more available in a more affordable way for more people.

I am disappointed of course, that the 2020 budget request would cut the agency by 13 percent. I am confident that this committee will not do that, but we will talk to you today about the reasons that we should continue in the direction we are in, rather than head in another way.

I am deeply concerned about an issue that I have seen develop, and I hope Dr. Collins, you have a chance to talk about that too. It is something that the research community needs to take more seriously, and that is that foreign governments are initiating systematic ways to influence our research, and frankly, to take advantage of our research by stealing it.

There is a Chinese Government program to recruit NIH (National Institutes of Health) funded researchers to encourage them to steal intellectual property; cheat the peer review system; establish shadow laboratories in China; and help the Chinese Government obtain confidential information about NIH research grants. That cannot continue to happen, and I look forward to hearing your discussion of that issue.

Obviously, there is an important balance here, of protecting our research from both foreign threats and other kinds of piracy and having the kind of collaborative environment you want to have to bring the best people into that research community you can. I know that is a challenge, and I have seen some challenges that you have faced even recently on that topic of who should be there and where they should be, but we benefited from them, they have benefited from us. This is a system that has worked, and we need to be sure we continue to protect it. Not everyone is well-intentioned.

I know there is an ongoing FBI investigation, and that it is investigating specifically what the Chinese government is trying to do to undermine our research structure. This is a serious threat to all of the things that make that structure work.

The NIH Advisory Committee has recommended several steps, including implementing a broad education campaign about the requirements to disclose foreign sources of funding, and developing enhanced cybersecurity protocols.

And while I appreciate those recommendations, I think that NIH has to be sure that the research community is fully aware of the threats, and more importantly, how to combat those threats.

NIH has sent only one letter to the community on the subject, but I am going to let you talk about that a little more either in your prepared remarks, or later in questions. It is a vulnerable environment. It is a critically important time to look to the future. A number of individuals that are part of the so-called Thousand Talents program may be few, but I think we should not just assume that that is the only program out there trying to do exactly the same thing, either.

So, Dr. Collins, certainly, I am pleased with the relationship you have had with this committee, with your leadership, I admire the team that you and your colleagues have put together. I am excited about the opportunity of the moment and glad you are here with us again today.

[The statement follows:]

PREPARED STATEMENT OF SENATOR ROY BLUNT

Good morning. Thank you, Dr. Collins and the Institute Directors, for appearing before the Subcommittee today to discuss the National Institutes of Health's fiscal year 2020 budget request.

As Chairman of this Subcommittee, re-prioritizing funding for the National Institutes of Health after a decade of stagnation has been my number one priority. Over the past 4 years, we have increased funding by $9 billion or 30 percent.

This increase has funded significant progress on vaccines for Ebola and Zika, developed blood tests to detect different types of cancer, and led to the first-ever drug specifically for postpartum depression. In my home State of Missouri, NIH research has demonstrated that interactive therapy can reduce rates of childhood depression, discovered an enzyme responsible for the spread of cancer, and supported research aimed at improving cancer immunotherapy.

I am disappointed the fiscal year 2020 budget request cut the agency by $4.9 billion or 13 percent. This is not a choice I will make when we write the fiscal year 2020 Labor/HHS appropriations bill.

While my commitment to biomedical research remains strong, I am deeply concerned about an issue I think NIH and the entire research community needs to take more seriously. Foreign governments are initiating systematic programs to influence the American research enterprise.

There is a Chinese government program to recruit NIH-funded researchers to steal intellectual property, cheat the peer-review system, establish shadow laboratories in China, and help the Chinese government obtain confidential information about NIH research grants.

I understand and support the need to balance protecting against foreign threats with the collaboration and open access that has long been prioritized in the medical research community. And in almost every case, talented foreign researchers have benefited the U.S. research community and moved medical research forward. As I have said many times, I believe that any foreign student coming to the United States for advanced education should be able to stay in the U.S. after that training is complete.

However, we must recognize that not everyone is well intentioned. We know from an ongoing FBI investigation that the Chinese government is trying to undermine the U.S. research infrastructure. This is a serious threat to NIH peer-review system, to universities and research institutions' intellectual property, and to corrupting a system that has long been held as the gold standard in research worldwide.

The NIH Advisory Committee has recommended several steps, including implementing a broad education campaign about the requirement to disclose foreign sources of funding and developing enhanced cybersecurity protocols. While I appreciate the Advisory Committee's recommendations, I do not think NIH has made the research community fully aware of the exact threats they face, and more importantly, how to combat them. In fact, NIH has only sent one letter to the community on the subject. The research community needs to understand that this is a serious, immediate, and specific threat, and that some foreign governments will use any means necessary to obtain a competitive advantage over the U.S.

In this vulnerable environment, I think it is prudent for NIH to be even more cautious about ensuring systems and protocols are in place to protect the research community. But I am unconvinced that is happening now.

Moving forward, I want to see clear steps taken to ensure all NIH grantees are trained to understand their roles and responsibilities within current policy. NIH needs to evaluate their peer-review system and internal controls through a lens that takes into account national security threats. And, finally, those who inappropriately share information from the peer-review process or illegally share intellectual property need to be held accountable.

While the number of individuals that are part of China's Thousand Talents program may be few, this program has uncovered a systematic flaw. We must take this threat seriously and NIH should take definitive steps today to maintain the integrity of the NIH system.

Thank you.

Senator BLUNT. I would like to turn to Senator Murray for her opening comments.

STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Well thank you very much, Mr. Chairman. Dr. Collins, good to see you and all of your team. Thank you to all of you for being here today and for the work you are doing.

The National Institutes of Health is perhaps the best example of an issue, where members on both sides of the aisle have been able to come together. We have repeatedly worked in a bipartisan way to provide increased investment in research that improves the health and well-being of people, invests in our local communities, and supports our Country's continued leadership in science.

NIH is the largest funder of basic research in the world and I am very proud that Chairman Blunt, thank you, and I, and others on this committee have been able to increase its budget by $9 billion over the last 4 years, despite opposition, by the way, from the Trump Administration.

Now we are here today to talk about President Trump's latest budget, and it stays true to form and proposes severe cuts across the spectrum of healthcare activities. In his budget, President Trump proposes steps that would undermine healthcare protections for 130 million people in this country living with a pre-existing condition. It strips healthcare away from tens of millions of people and we should not forget he is arguing in court for a ruling that would do all of that and more.

President Trump's budget proposes slashing the Centers for Disease Control and Prevention, including their work on birth defects and disabilities, their efforts to combat antibiotic resistant pathogens, and emerging infectious diseases and more. It slashes funding for the healthcare workforce training programs at a time when our Nation is facing a healthcare provider shortage, particularly in our rural areas, and it proposes eliminating funding for the Teen Pregnancy Prevention Program and cutting funding for rural health and maternal and child health.

And at a time of remarkable possibility in medical research, a time where we can and should continue leading the world in medical discovery, the Trump administration wants to cut funding for NIH.

President Trump's budget offers one small step forward for pediatric cancer research and a marathon sprint backward for everything else.

While he proposes increasing pediatric cancer research by $50 million, he proposes cutting $100 million, twice that amount, from diabetes research. He proposes cutting $300 million, six times that amount, from Alzheimer's research, and he proposes cutting over $1 billion, 20 times that amount, from efforts to discover treatments for every other kind of cancer. In fact, for every new penny President Trump proposes for pediatric research, he proposes cutting a dollar from NIH. He would cut funding from just about everything, which would mean delaying, or even missing opportunities to find treatments and cures that could save lives, like a universal flu vaccine, or a vaccine for HIV.

President Trump's damaging budget is wildly out of step with the sentiments of Congress, thankfully, and the American people, and I feel confident working with our chairman that we will once again reject it.

Now, I do want to say that with that support for NIH, however, comes the expectation that NIH will lead in all the fields in which it is involved, including setting the highest standards for the behavior of the research community it funds.

Last summer, the National Academies of Science, Engineering, and Medicine released a report that found sexual harassment is common in all three fields.

Dr. Collins, you and I have had numerous discussions about this. The report found that almost half of women in medical school or enrolled as a graduate student in a college of medicine, and more than half of women faculty in academia reported having experienced some form of sexual harassment.

The Academies recommended Federal research agencies require institutes to report when people on grants have violated sexual harassment policies or have been put on administrative leave due to harassment allegations. A recommendation the National Science Foundation has since adopted.

NIH needs to step up and demonstrate greater leadership in holding its partners and extramural grantees accountable, as well. It is not acceptable for NIH to defer to its grantee institutions or other agencies to address harassment, rather than actually requiring them to report when it happens in research settings, or by researchers funded by NIH grants, especially when NIH's funding gives the agency such sway with the research community.

Harassment undermines scientists and researchers professional and educational obtainment and erodes the integrity of the research enterprise. It makes survivors feel inferior or that they do not belong, and it draws promising young scientists away from research at great cost to our Nation and our scientific advancement.

I expect more from NIH on this issue, and Chairman Blunt and, Dr. Collins, I would like to work with you both on direction that requires NIH to take meaningful action to address harassment that occurs in both intramural and extramural settings, including implementing recommendations from the Academies report, some of which the National Science Foundation has already done.

Thank you, Mr. Chairman.

Senator BLUNT. Thank you, Senator Murray. As Senator Murray pointed out, the committee has worked hard on this together, as Senator Durbin, Senator Alexander, great advocates, along with

Senator Shaheen, and Senator Moran, but the two people at the top of the committee have also been incredibly important in encouraging us to move forward.

I might point out that it is not just the current budget, the past administration actually proposed cutting NIH research at a time or two, and never proposed, as far as I know, increasing it, at least it did not get increased. So, we have sort of had a bipartisan determination to correct a bipartisan failure to move forward for a long time. We are going to continue to do that and one of the reasons we will be able to do that is the great leadership of the Chairman, who joined us today.

And Chairman Shelby, do you have some comments?

STATEMENT OF SENATOR RICHARD C. SHELBY

Senator SHELBY. Thank you. Thank you, Chairman Blunt, Ranking Member Murray.

First, I would like for my written statement to be made part of the record.

Senator BLUNT. Without objection.

Senator SHELBY. And I will be very brief. I am going to tell you, and I agree with those Senator Blunt and Senator Murray, this is an important hearing. What you do is more important than most of what we do in America. I am not interested in cutting your budget, I am interested in increasing it; so, are they. We are going to have a big struggle this year, dealing with the budget, but I think this is a great investment for America, for the world, for humanity, what you do.

Sitting at the table here, all of you distinguished in your own right; we are fortunate to have you, to have your dedication and we are going to stay with you, and we are going to continue to do it.

I believe it is not only a financial investment, which is good for the economy, it is the leading scientist at cutting edge of scientific research that you had. We all benefit from it immensely.

Thank you, Mr. Chairman.

[The statement follows:]

PREPARED STATEMENT OF SENATOR RICHARD C. SHELBY

Dr. Collins, I want to thank you and your colleagues for coming today to give us updates on the great work that you are doing at the National Institutes of Health (NIH).

I have enjoyed our conversations in the past about the importance of research, and I applaud the job that you have done as Director of the NIH.

Research institutions in Alabama have done some wonderful advancements with the funding they receive from the NIH.

Not only do our institutions in Alabama reap the benefits by attracting the brightest minds to perform the research, but the Alabama economy as whole capitalizes on the above average wages of researchers and the buying power they add to local businesses.

It is important to Alabama and the rest of the country that we continue to increase funding for medical research at the NIH. America needs to remain at the forefront of advanced medical research, and investigators want to know that Congress is committed to pursuing new treatments and cures.

Thank you all for coming today, and I look forward to asking you some important questions.

Senator BLUNT. Well, thank you, Chairman.

Again, Dr. Collins, welcome to you and the directors of several of the institutes that are with you today. We look forward to hearing what they have to say as well, but if you would like to start with your opening statement, this would be the time to do that.

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

Dr. COLLINS. Well, thank you.

Let me introduce the people at the table. On my left, your right, starting over at the end, someone well known to this particular panel of Senators. We estimate this might be about his 400th hearing, Dr. Tony Fauci, Director of the National Institute of Allergy and Infectious Diseases.

Next to him our Director of the National Institute on Aging, Richard Hodes. Then next to me, Dr. Griffin Rodgers, Director of the National Institute of Diabetes, Digestive and Kidney Diseases. On my right, Jon Lorsch, Director of the National Institute of General Medical Sciences. Next Doug Lowy, who has stepped back into the role as now Acting Director of the National Cancer Institute, as Dr. Sharpless has moved over to FDA (Food and Drug Administration) just in the last few days. And then on the end of the table, Dr. Nora Volkow, Director of the National Institute on Drug Abuse. I am honored to have these colleagues with me today for what I hope is going to be a really important exchange of ideas and information.

So, Chairman Blunt and full committee Chair Shelby, Ranking Member Murray, members of the subcommittee, I want to thank you most sincerely for your strong and consistent, and bipartisan support of NIH. In fiscal year 2019 we received a most welcome increase of $2 billion, enabling us to continue our mission of turning scientific discovery into healing and hope, and we will have a chance to tell you about some of those things in the course of this hearing.

I take very seriously the comments that were raised by the Chairman about foreign influence, and by the ranking member about sexual harassment. These are issues of incredible intensity and importance and I hope we can discuss some of those in the course of the questions.

But I wanted to introduce you today to just a few of the millions of people who over the years have made medical research progress possible by volunteering to take part in NIH funded research. Instead of focusing on the researchers, I am going to focus on our really important partners, the people who take part in these clinical studies, and tell you something about three examples of them.

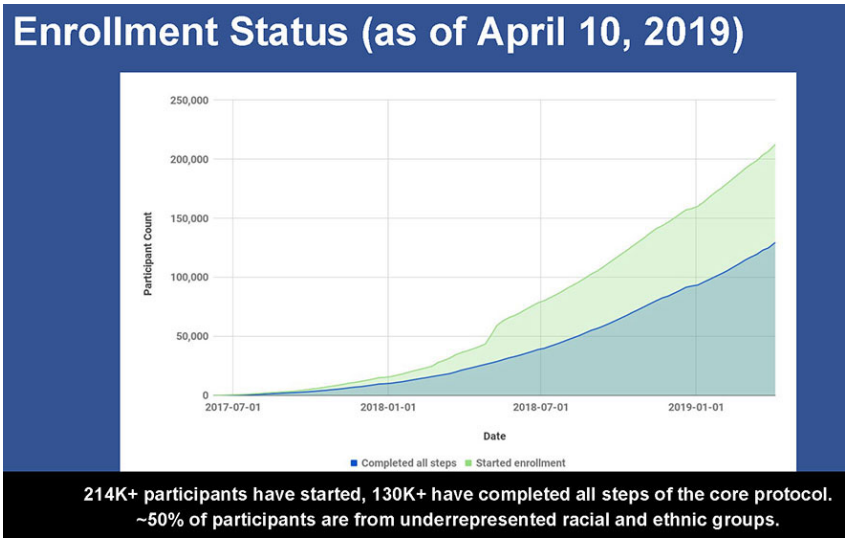
[The graphic follows:]

Let's begin with Richard Hockfelder. Six years ago, this retired aerospace engineer had a blood test called hemoglobin A1c that showed that he was at high risk of developing diabetes, a pre-diabetes diagnosis. So, he took some preventative steps like cutting down on carbohydrates and exercising more to get his health back on track and that work really well.

[The graphic follows:]

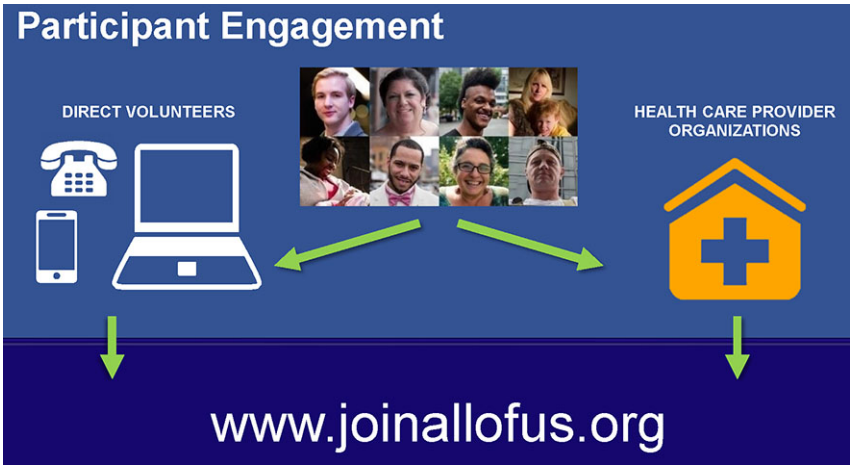
Now he could have kept that success to himself but instead he decided to help others and he joined NIH's All of Us research program, which is building an unprecedented resource to explore what health approaches work best for each individual, and why. This is precision medicine on a scale we have never attempted before.

[The graphic follows:]



We are making great progress toward enrolling our goal of 1 million or more people. And you can see from the graph where we are in less than a year, more than 200,000 people have, in fact, begun enrollment, and about 50 percent of those are from traditionally underrepresented racial and ethnic minority groups. Because we want very much to have an opportunity with this resource to understand health disparities, it is a very diverse population.

[The graphic follows:]

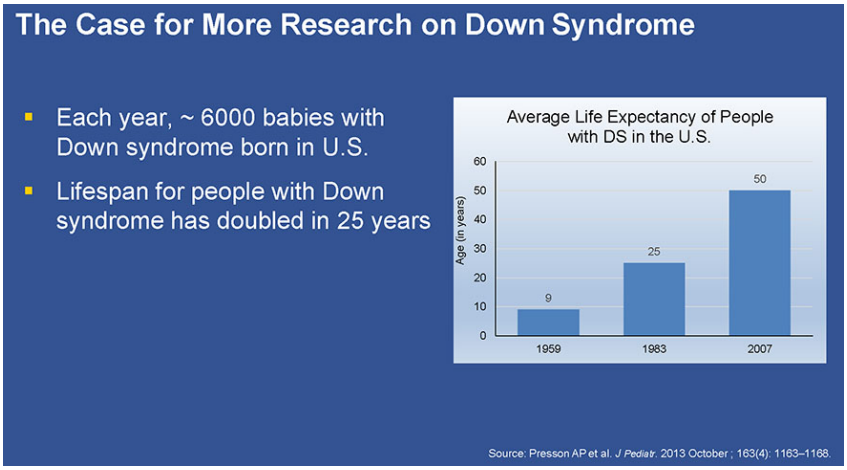


Now all the information that they contribute of various types, will go into a highly secure database that researchers can get access to, to make discoveries. Success is going to depend on involvement of people from all walks of life, so we encourage you to join too. All you have to do is go to joinallofus.org, and anybody in our country can join this effort. And we do hope by the next 3 years to take this already quarter of a million and bring it to a million people. This is unprecedented. It is already the largest study that we have mounted in a very long time and we are only a quarter of the way there.

[The graphic follows:]

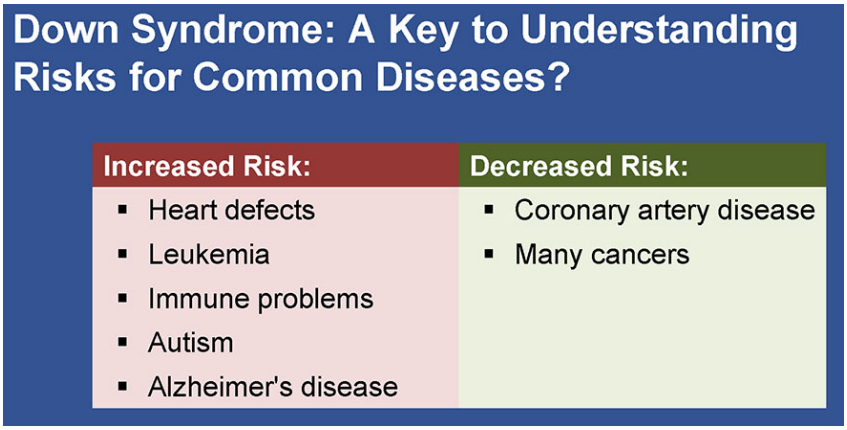
Let me turn to another example of somebody who has volunteered to help us with research. This is Frank Stevens. Frank belongs to a community with unique biological characteristics that has been offering to volunteer for research for years, but too often has not really had that opportunity. I am talking about individuals with Down Syndrome. We need to do better for them.

[The graphic follows:]



Frank actually did testify before Congress in October 2017, that is where this picture is taken. Now Down Syndrome usually results from having an extra chromosome 21, each year about 6,000 babies are born with this condition in the U.S., and the average life span has doubled in recent years, but these folks still face significant health challenges. They include an increased risk of heart defects, of leukemia, of immune problems, of autism, and Alzheimer's disease.

[The graphic follows:]



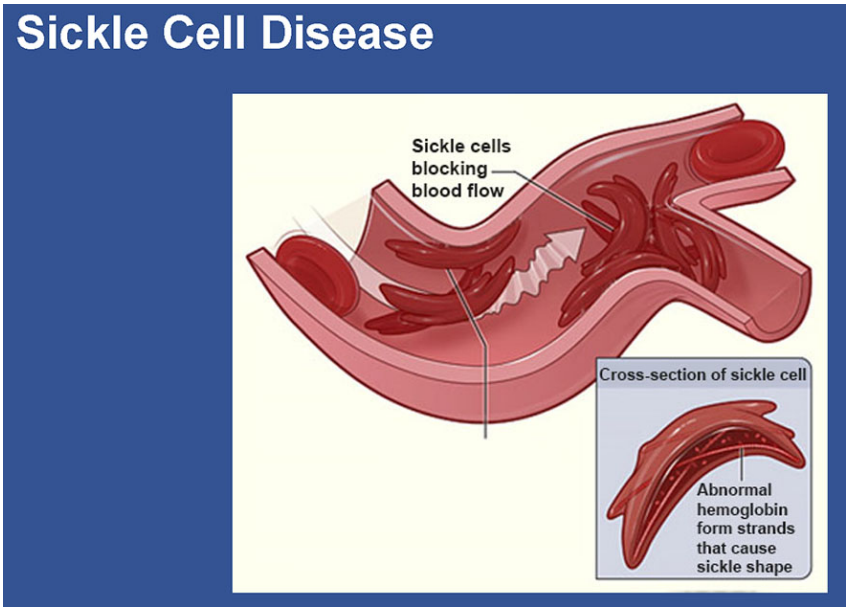
On the other hand, interestingly, Down Syndrome individuals have a lower risk of coronary artery disease and a lower risk of solid tumors, even when you age-match. We do not know why that is and it would be very important to figure that out.

So, because of this studying Down Syndrome may hold the key not only to helping those who have the condition, but also to understanding common diseases in all people. And this is a good example how rare diseases can inform about things that go well beyond that particular condition. NIH is stepping our efforts to do just that.

[The graphic follows:]

This should come as good news to Frank and his Mom, you see here vacationing, and his mom Cornelia, actually herself, has already shown signs of Alzheimer's disease. Frank faces a greatly increased risk of that because of his Down Syndrome, but his Mom already has it, and he wants to try to help her as well. As Frank once put it, "My extra chromosome provides a blueprint for medical research that could reveal answers to this heartbreaking disease."

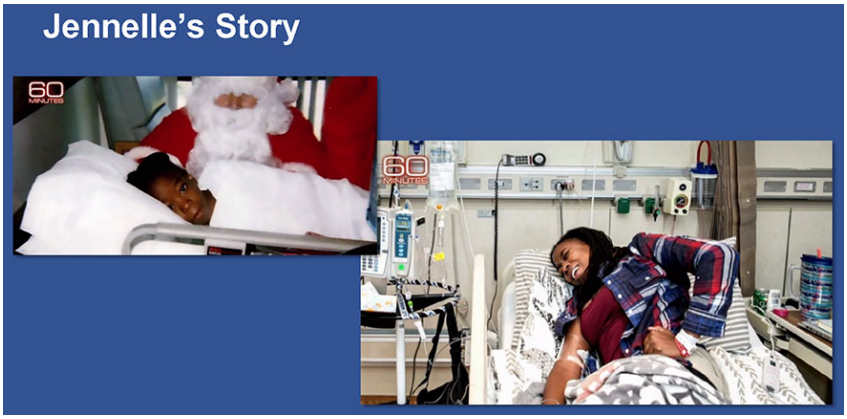
[The graphic follows:]



Well speaking of heartbreaking diseases, I told this subcommittee last year that we might be on the verge of a cure, I used the C word, cure, for sickle cell disease. A life-threatening genetic disorder that bends red blood cells into a sickled shape because of a mistake in the gene that codes for one of the hemoglobin proteins, and they are bending then into this sickled shape that blocks blood vessels, causing excruciating pain in a sickle cell crisis, and damage to organs, which sadly shortens the lives of people with this condition, substantially.

So, we talked about last year, maybe we are on the brink of something, today I am thrilled to say, I think we have reached a remarkable milestone.

[The graphic follows:]



Let me introduce you to Janelle. Janelle Stevenson is one of the brave research participants who has helped make this happen and whose story was recently featured on CBS's 60 Minutes. Throughout her young life, as you can see, she was often hospitalized, even at, Christmas; you see there with Santa Claus next to her bed and has experienced over the course of her 20 years, just about the worst pain that a human can imagine from these crises.

[The graphic follows:]

But she decided to take a bold step for herself and for others with this condition and signed up for a gene therapy trial at the NIH Clinical Center. This trial, her own bone marrow stem cells were removed; modified to compensate for that sickle mutation, and then infused back into her body where they began producing healthy red blood cells. The transformation has been pretty incredible.

Here is Janelle, sitting alongside her father, Ray wearing her white jujitsu uniform. And here she is—remember this is somebody who was pretty much almost bedridden before this procedure [Video shown].

So, our Nation needs a lot more stories like this, but that one certainly heartening to anybody who has wondered are we going to come to an answer for that first molecular disease, sickle cell. We have known about it for more than 100 years and now, a molecular cure for that molecular disease in a very rigorous research protocol, and the treatment was challenging to endure, but you can see this is working.

The promise is now real for the nearly 100,000 Americans who suffer from this devastating disease.

[The graphic follows:]

So, we need a lot more stories like this through the generosity and courage of people like Richard, Frank, and Janelle, along with your strong and sustained support. NIH research is making it possible for these kinds of stories to emerge every day and the world can look forward to a healthier and happier future.

So, thank you, Chairman. We welcome your questions.

[The statement follows:]

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

Good morning, Chairman Blunt, Ranking Member Murray, and distinguished Members of the Subcommittee. 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 Budget request for the upcoming fiscal year and some of the exciting scientific opportunities on the horizon, I want to express my gratitude to the leadership and members of this Subcommittee. In fiscal year 2019, NIH received an increase of $2 billion.I can promise you that we are investing those resources in groundbreaking research as quickly as we can.

Biomedical research at NIH seeks to push forward the frontier of knowledge, from basic science to translational research to clinical trials, and success relies on vision, risk-taking, and a tireless pursuit of the next scientific question. NIH will continue to invest in people, programs, infrastructure, and technology with these goals in mind, consistently striving for breakthroughs that culminate in improvements in human health and wellbeing. From harnessing new technologies to supporting the next generation of researchers, NIH will invest its resources to ensure that the U.S. remains at the forefront of innovation and discovery.

The fiscal year 2020 President's Budget provides $34.4 billion for NIH, seeking to fund the highest priority scientific discoveries while also maintaining fiscal stewardship of Federal resources. This Budget will prioritize biomedica l research to confront our Nation's greatest medical challenges, including the opioid crisis, precision medicine, and pediatric cancer.

As in previous years, the Budget proposes to streamline Federal research by consolidating activities of the Agency for Healthcare Research and Quality (AHRQ) into a new National Institute for Research on Safety and Quality (NIRSQ) within the NIH. The Budget provides NIRSQ $256 million to support its activities to improve the quality, safety, effectiveness, and efficiency of healthcare.

America's continuing leadership in biomedical research requires infrastructure and facilities capable of housing safe, reproducible research in compliance with all laws and regulations and conducive to cutting edge research. NIH buildings include inpatient hospital beds, Biosafety containment facilities, biomedical research labora-

tories, animal holding facilities, and even a utility plant. NIH's backlog of maintenance and repair now exceeds $1.8 billion.

NIH is aggressively using fiscal year 2019 funding to address some of this backlog and ensure our facilities are both safe for patients and conducive to cutting-edge research and research support. The fiscal year 2020 Budget invests in NIH's facilities by again proposing $200 million to support multiple biomedical research infrastructure priorities at NIH-owned sites.

One of my personal priorities since joining NIH has been to develop and support the next generation of biomedical researchers. In August 2017, NIH launched the Next Generation Researchers Initiative to address the challenges faced by researchers trying to embark upon and sustain independent research careers. I am pleased to report that NIH met its ambitious goal of funding 1,100 early-stage investigators in fiscal year 2018. In fact, we funded 1,287, the largest number in history. The fiscal year 2020 Budget includes a dedicated fund of $100 million in the Office of the Director to support the prioritization of meritorious applications to support early stage investigators that have never been funded by an award, or current NIH- supported researchers at risk of losing support. NIH remains committed to the development, support, and retention of our next generation of investigators.

This is a remarkable time in biomedical research. Truly exciting, world class science is taking place through NIH support, and leading to breakthroughs in multiple areas. I would like to provide just a few examples of the depth and breadth of the amazing research the fiscal year 2020 Budget supports.

The fiscal year 2020 Budget continues to invest in Precision Medicine. Less than 1 year ago, NIH formally launched national enrollment for the All of Us Research Program. This program is on pace to enroll one million or more U.S. volunteers in an ambitious effort to accelerate health research and medical breakthroughs. With this Committee's long-standing support, we are closer than ever to building the most diverse biomedical data resource of its kind. By analyzing individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine, an emerging approach for disease prevention and treatment.

As of April 7, 2019, more than 212,000 people have begun the enrollment process, and more than 129,000 have completed all the steps in the protocol. The All of Us Research Program is committed to engaging individuals from all walks of life, including those who may not have been asked to participate in research previously, and more than 75 percent of participants are from communities that have been underrepresented in biomedical research. This diversity has the power to revolutionize standards for inclusivity in research and for generalizability of biomedical research findings across many communities, with the ultimate goal of spurring discoveries that bring the promise of precision medicine to all of us. The fiscal year 2020 Budget provides $313 million to support the All of Us Research Program.

Millions of Americans across the Nation have been devastated by opioid misuse, addiction and overdose. To help bring scientific solutions to this crisis, and to provide safe and effective options for the more than 25 million Americans who suffer from daily chronic pain, NIH launched the Helping to End Addiction Long-term (HEAL) Initiative. This Committee made a historic investment of $500 million in our work in fiscal year 2018 and built upon that investment in fiscal year 2019 with an additional investment of $500 million. Through HEAL, NIH will build on basic science discoveries to accelerate the development of novel medications and devices to treat all aspects of the opioid addiction cycle, including chronic use, withdrawal symptoms, craving, relapse, and overdose. NIH has launched a series of new studies to test both new non-addictive medications and non-pharmacologica l strategies for pain management, with the goal of targeted treatments for the millions of Americans living with chronic pain. The fiscal year 2020 Budget continues the special investment of $500 million that was started in fiscal year 2018, and supports a total of $1.3 billion for opioids and pain research across NIH, ensuring that we continue to respond aggressively to the crisis of pain and addiction in our communities.

Cancer is the leading cause of death from disease among children and adolescents in the United States. Although substantial progress has been made in the treatment of several types of childhood cancer, progress against other types has been limited. Even when long-term survival is achieved, many survivors of childhood cancer may experience long-term adverse effects from the disease or its treatment. More research is needed to develop new, more-effective, and safer treatments for childhood cancer. The President recently launched an initiative to support pediatric cancer research. The fiscal year 2020 Budget provides $50 million for a data initiative that will support the development of new, more effective, and safer treatments for childhood cancers, and will facilitate aggregation of data to create a federated, comprehensive, and shared resource to support childhood cancer research.

First identified in 1981, AIDS is one of humanity's deadliest and most persistent epidemics. Although significant progress has been made in the fight against new infections and AIDS deaths, the HIV/AIDS pandemic continues around the world. The development of a safe and effective HIV vaccine remains a key component to realizing an end to the HIV/AIDS pandemic. The NIH-wide HIV research program will continue to sustain the accomplishments already made and secure future advances to prevent the spread of HIV; improve health outcomes for persons with, at risk for, or affected by HIV; and ultimately to find a cure for HIV. The fiscal year 2020 Budget includes $6 million for NIH to support the President's Ending HIV Epidemic Initiative. The NIH-funded Centers for AIDS Research and AIDS Research Centers are leveraging critical relationships with local and State public health services, communities, and research institutions to develop and refine evidence-based, community-specific strategies that will help guide this initiative.

The fiscal year 2020 Budget continues to invest in research progress toward the important but scientifically challenging effort to develop a universal influenza vaccine. NIH-supported research is helping advance understanding of how influenza strains emerge, evolve, infect, and cause disease. These research results are informing design of new and improved therapies, diagnostics, and vaccines. Influenza viruses pose an ever-present public health threat and place substantial health and economic burdens on the U.S. and the world. The fiscal year 2020 Budget will accelerate research progress to achieve the end goal of a universal influenza vaccine, which is vital to protecting millions of people from infection and mitigating the public health threat posed by influenza viruses.

NIH is at the vanguard of biomedical research, leading the world in support of groundbreaking science. Thank you again for inviting NIH to testify today. We look forward to answering your questions.

FOREIGN INFLUENCE

Senator BLUNT. Thank you, Dr. Collins.

Why don't we talk a little bit about the efforts you have made on the concern about foreign involvement, about duplicate labs in other countries, and information being shared that should not be, and then what we are going to do about it.

Dr. COLLINS. I would be glad to do that. We are deeply concerned about the evidence which has been growing and which we have become increasingly aware of over the course of more than a year, that there are instances, egregious instances, where our funding of grants in this country is being taken advantage of by individuals who are not following the appropriate rules. This is utterly unacceptable.

We have had multiple opportunities to interact with the FBI, who have been investigating this vigorously. Some of this is classified information, some of it is not. And as a result of that have uncovered what has now led to more than 55 investigations that are ongoing of institutions where we believe there may be investigators who are double dipping, receiving foreign government money without disclosing it, or in some instances, diverting intellectual property that was rightly the property of the institution where they are working, to China. Or, maybe most egregiously at all because it violates such an important principle for us, taking grants that they are asked to review as part of the peer review process and distributing those to another country even before those grants have gone through the full review process, giving therefore an opportunity for somebody else's ideas to be stolen.

Knowing the seriousness of this, I did something unprecedented and wrote—first time since I have been NIH director, to every one of our grantee institutions, and that is more than 10,000, a very strongly worded letter saying this is an issue they all need to take with great seriousness, and if they are not aware of what their own

faculty are doing in terms of these kinds of relationships, need to begin to find that out.

I think there was initially some surprise and maybe even denial that that could be happening in these institutions. I think we are past that now and we are now seeing statements from some of those institutions, very strongly worded to their own faculty saying, we realize we have a problem too. There increasing instances where faculty members have been fired, have been asked to leave the institution, many of them then, returning back to their previous foreign base. And I should say while China has certainly been mentioned a lot, this is not only China.

So, actions are being taken and you will see more evidence of that in the press, and particularly in the coming week or two, to show just what is now necessary in order to respond to this. We will not rest until we have looked at every possible example. We have to depend on the universities as our partners in this, but we are driving this process as vigorously as we can.

Senator BLUNT. Within those 55 instances, how many different institutions would that involve?

Dr. COLLINS. That is 55 institutions.

Senator BLUNT. 55 different grantee institutions?

Dr. COLLINS. Yes, and basically, we are triggered by noting in a grantee that there is a publication that comes out that seems to involve a lot of authors and a lot of other institutions that were not mentioned in their grant applications. Now, maybe that is an appropriate collaboration; I am not going to tell you that every one of these investigations is going to reveal something bad happened, but some of them will.

Senator BLUNT. Well, we clearly benefit from having people from other countries here; to have their skill level here. Frankly I think we benefit to have them, if they want to stay here, to let them stay here.

Dr. COLLINS. Absolutely.

Senator BLUNT. It is difficult to look at this from the point of view of where somebody comes from, but no matter where they come from, if they are involved in this, we are going to have to obviously be at a higher level of on-guard, than we have been.

Dr. COLLINS. Mr. Chairman, I am totally with you, as are my colleagues. I am glad you raised, though, the concern though that we not carry this to the point where anybody who is a foreign national begins to feel like they are under suspicion, even if they are honorable contributors to our workforce, because almost all of those folks are. We need to be careful that we do not step into something that almost seems a little like racial profiling.

I think Chinese scientists working in the U.S. have already written some letters to Science Magazine to express their concern about not being swept into this same framework where everybody is under suspicion, because the vast majority of these folks have been incredibly important and honorable contributors to our workforce.

Senator BLUNT. Now, there is a research synergy that you achieve by bringing people together from totally different preparation, styles, and everything else into that research moment, I think.

Dr. COLLINS. Yes. Diversity contributes to productivity in every way, and all kinds of diversity that is true, including gender diversity, including people from different socioeconomic backgrounds, and from different countries.

Senator BLUNT. Yes. I am sure we are going to have lots of questions. Let's try to stay with the 5-minute time, but we can, anybody that wants to stay beyond their first round, we will get to as many questions as we can possibly get in between now and the time we are done.

Senator MURRAY.

DATA COMMONS

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

You know, many research organizations are now exploring the best ways to create research data commons. Private sector communities of companies and extramural research institutions like, science bound networks, Penn State, and Google's datacoms.org have demonstrated success, while other Federal agencies are already further along than NIH in successfully establishing data commons, like the National Science Foundation big data innovation hubs. It is really important that we learn from them, as well as from some less successful attempts at driving data instruction, like CA Bigg, which saw very little traction in the community and was widely criticized.

So, Dr. Lorsch, let me start with you. What is NIH doing to avoid reinventing the wheel, and how is NIH planning to leverage data commons work that is already being done extramurally?

Dr. LORSCH. Thank you very much Senator. That is a very important question. If we can connect disparate types of data, so, say data from the Jackson Heart Study with data from Dr. Hodes' Alzheimer's disease databases, the power of that could be enormous in terms of generating new ideas, new connections between these diseases, or in that case, between cardiovascular health and dementias, for example. That might lead to new ideas about treatments that could be possible or earlier detection strategies.

This is what we call interoperability, making data that is in different languages, essentially, able to talk to each other so the scientists can use that data for these kinds of discoveries.

We are working very closely right now with our partners in academia, as well as experts in the tech industry, particularly through the STRIDES Initiative, which is an arrangement with Google and Amazon that we have right now, to develop ways to connect the high-value data sets that NIH has, the Jackson Heart study, for example and Alzheimer's data together, to create this interoperability.

We are definitely looking at past examples, both successful and unsuccessful, to help guide us, and we are definitely taking a lot of input from experts, particularly in the tech industry through that STRIDES initiative.

DATA SCIENCE IN OTHER FIELDS

Senator MURRAY. Okay. Dr. Collins, what is the agency doing to really encourage and support data science training in other sci-

entific fields beyond those like genomics and neuroscience, which really have embraced this?

Dr. COLLINS. I appreciate that you are raising this issue, and John Lorsch has been very much a leader in the space.

You see here our website, which will show you our strategic plan for data science, which has been a way in which we have tried to put together a lot of ideas. I totally take your point about not reinventing wheels that have already been tried either successfully, or otherwise. So, I think we are pretty well invested in that.

And certainly, a big part of this is training. We are seeking to bring more fellows to NIH to bring the skill sets that exist in Silicon Valley and get them excited about biomedical research, because that is where a lot of the talent is. We are recruiting a chief data strategist, probably somebody from the private sector, to help us with that kind of culture change and recruiting of talent that we know we need. We need our bench to be a lot deeper, we aim to get it there.

Senator MURRAY. Okay, good. Thank you. I really appreciate it.

NCI AWARD PERCENTAGES

Dr. Lowy let me turn to you. While Congress has been providing the NIH, including the National Cancer Institute, with more funding each of the past 4 years, the odds of securing a grant from NCI (National Cancer Institute) have actually been getting more difficult. Can you tell us what is driving that trend and what its significance is, and do you expect it to continue?

Dr. LOWY. Thank you very much, Senator Murray. Thanks to the generosity of Congress, we have received an increase in our appropriation for the last several years, approximately 17 percent through 2018, to the regular appropriation during that time. During that time we have increased the number of awards made for investigator initiated research by about 20 percent, the number of new people in the awards system and the NCI by 20 percent, and so this is, I think, very much in line with what you and your colleagues have had in mind.

On the other hand, we have had over that period a 50 percent increase in the number of grant applications, and so it has not been possible to keep up with the number of awards that we would like to make, although we are very pleased we have been able to make more.

It has led to the success rate for investigator-initiated research going from 15 percent down to a little bit below 12 percent during that time period, and we certainly hope that we will be able to increase the success rate going forward. For example, this year we are planning to put in more money to the RPG (Research Project Grant) pool than even with the generosity of Congress is, has added to the NCI regular appropriation.

Senator MURRAY. Okay thank you, very much. I appreciate that.

Senator BLUNT. Senator Shelby.

PUBLIC SECTOR PARTNERSHIPS

Senator SHELBY. Thank you.

Dr. Collins, you previously said that the private sector research outspends public sector research three to one; three to one. To pre-

vent overlap, investigators in the public and private sector, I believe, should coordinate research where they can so that efforts would not be duplicated so much. I know there is an accelerated medicines partnership, AMP, going on, you have talked about it before. Would you give us an update on this and how we are working together to get the good results?

Dr. COLLINS. I am happy to talk about that. Yes, I think it is a great opportunity to bring the best and brightest of skill sets in terms of scientists and also the areas of expertise. NIH is in the basic science in translational arena, but we do not make pills and the industry does, and we have to figure out how to do that handoff so that this ecosystem really flourishes.

I get invited each year to a meeting of the heads of research and development of the largest pharmaceutical companies; we just met this past weekend. And we have developed, I think, a very functional working relationship there to identify opportunities for shared collaborative precompetitive efforts, and AMP that you just mentioned, the Accelerating Medicines Partnership, is one of those which I think has been particularly successful.

This allowed us to come together around several diseases, and that includes Alzheimer's disease, and rheumatoid arthritis, and lupus, and diabetes, and basically to work together to identify whether there were areas that we could as a group do, that neither could do alone, yet make all the data available. We have to do that, we are NIH.

In those projects which are now almost 5 years along, we have met every milestone, and everybody who is involved would say we have accelerated the progress in finding new treatments for those diseases.

Everyone is a little different in terms of the particular science that is being supported. My colleagues here are a part of that so, Dr. Rogers oversees the NIH part of the diabetes effort, Dr. Hodes oversees the part of the Alzheimer's effort, Dr. Carter, who is not here, the rheumatoid arthritis and lupus, and we have just started a new one on Parkinson's. And we are talking about a new one on schizophrenia where we desperately need some new ideas, and industry after being a little reluctant before, is now looking as if they could embrace that, too. There is a separate project on cancer immunotherapy called PACT, which is a relationship we have with industry.

I think we are finding ways, obviously recognizing we have different goals, to make that happen and that is a personal priority for me to be sure we do not miss those opportunities.

CYSTIC FIBROSIS

Senator SHELBY. What about cystic fibrosis? Where are you going there, and where do you hope to go? You have come a long way.

Dr. COLLINS. Well, this is also something I have a personal passion about, having had the opportunity to co-discover the gene for cystic fibrosis exactly 30 years ago. And now to see, although it took 30 years and I wish it had been faster, the emergence of highly effective, triple therapy with a very well designed molecular-based drugs that looks as if something like 90 percent of people with cystic fibrosis are now going to have a treatment that allows

them to live out what could be almost normal lives. Which is an amazing thing to be able to say.

It took a huge amount of work from NIH funded resources to try to figure out exactly what the mechanism is for this disease, and what kind of drug might work, and then a close partnership with a company called Aurora which then became Vertex, and now here we are. And it is incredibly gratifying to see that for all those kids and families that have been waiting for this all this time.

Senator SHELBY. Doctor, you have been very involved in the National Center for Advancing Translational Sciences, and so forth.

Dr. COLLINS. Yes.

RURAL HEALTHCARE ACCESS

Senator SHELBY. Could you elaborate on how NIH is implementing this program to address healthcare access and delivery in rural areas across the country?

Dr. COLLINS. So NCATS, the National Center for Advancing Translational Sciences, is one of our newest entities. I have been very excited to see this emerge, trying to identify ways that we can help research projects that sometimes get stuck in the valley of death actually move across for benefit to people out in the clinics and the hospitals.

NCATS also runs the CTSAs, the Clinical and Translational Science Awards, which is this network of 57 centers across the country. But we are aware that those are generally located in more urban settings and there is an opportunity and a responsibility to reach out to rural communities.

NCATS has out right now, a notice of interest out there to think about how to link up in that way. One possibility is to link up with the idea states clinical trial research networks, which are also often times more in an opportunity where there is a rural setting. And also, to see if there is a way to work in the pediatric clinical trial network which is also been put forward as part of the effort to deal with the opioid crisis.

So, we have a lot of connections here that are being built. There was a meeting at the University of Florida to talk about this two days ago, I am waiting to hear what the results of that were.

FUNDING LEVELS

Senator SHELBY. Doctor, lastly, could you explain how NIH determines funding levels for research within its larger funding number, because all of us advocate for certain diseases that touch us and touch our friends and family, and constituents in many ways.

Dr. COLLINS. In the minus 21 seconds I have, let me see what I can do to outline.

[Laughter.]

Senator SHELBY. Well, I think I am over.

Dr. COLLINS. It is a critically important question. All of us around this table work with that issue virtually every week trying to be sure we have our priorities set. I might point you to the strategic plan that we put forward a couple of years ago, which tries to go through in a very clear fashion how those priorities get set.

May I say, we appreciate the fact that the Congress generally does not give us a lot of recommendations about specific disease

areas, because we think science is in the best place to make those decisions along with what the public health need is, and that is what we try to do every day.

Senator SHELBY. Mr. Chairman, could I just, not a question, make a request? Dr. Vickers invited you to be the keynote lecturer, I am sure all over the world, but in Birmingham and at the lecture, Academic Leadership Medicine, Academic Leadership Series. I hope if you can work that out you would go; you have been there before. They asked me to do this and I told them I would follow their request.

Dr. COLLINS. I will be there.

[Laughter.]

Senator SHELBY. Okay. Thank you.

Senator BLUNT. That is the right answer, I am sure.

[Laughter.]

Senator BLUNT. Senator Durbin.

Senator DURBIN. Once again proving all politics is local.

RESEARCH INTEGRITY AND STEWARDSHIP

Dr. Collins, it was about 5 years ago when I visited the NIH and you and I had a conversation which informed and inspired me about 5 percent real growth a year in funding on medical research. The education of a United States Senator is a daunting task, and I thank you for taking the time to explain to me how consistency is as important as amounts.

It is a new challenge to you too, in this day and age, to justify the amount that is being added each year when I look at the record. And I want to give special shout-outs to our Chairman here, Senator Blunt, Senator Murray, who just in both authorizing and appropriating committees, has been a national leader on the subject, and Senator Alexander who is retiring. I am hoping that someone with his skill and determination will replace him to continue this battle, but since fiscal year 2014 we have seen the 30.6 percent increase in NIH funding, a 40.6 percent increase in Department of Defense medical research and a 33 percent increase in VA (Department of Veterans Affairs) medical research. The CDC (Centers for Disease Control and Prevention), 7.4; I wish it could have been more because it is a deserving agency.

But when you answer the question of the Chairman about the integrity of the research undertaking and endeavor, particularly our concern about falsification of data or the stealing of information, I think it really goes to the heart of this. Those of us who deeply believe in what you are doing and believe it is one of the most important parts of our public lives, really need to count on you, as well, to join in in proclaiming that integrity is not being compromised and money is being well spent. Our critics are going to be watching to find evidence to the contrary.

Would you like to comment on that?

Dr. COLLINS. I could not agree more. Let me say, I appreciate your beginning your comments about this importance of predictable, steady trajectory for support that has been such a source of encouragement, particularly to young investigators who are seeking to know whether they had a path for their careers.

And frankly, things were looking pretty tough for them, 6 or 7 years ago as we had lost a fair amount of purchasing power. Now to have this, 4 years in a row of a steady upward trajectory, has changed the dynamic completely in the institutions that I go and visit, where the postdocs, and the graduate students, and the junior faculty are now really fired up about the opportunity.

But you are right, this puts great responsibility on us to be stewards of every dollar of that and if we find misuse of that information, to move swiftly to make sure that that is quickly stopped. We are doing everything I think we can in that regard, with help from our institutions to root out that problem and I think we have made a lot of progress, but we are nowhere near done.

AMYOTROPHIC LATERAL SCLEROSIS

Senator DURBIN. I would like to get more specific and personal in this next question. Tuesday morning a young man from Chicago named Brian Walleck, and his wife Sondra came in to see me. A year and a half ago, 18 months ago, he was diagnosed with ALS, Lou Gehrig's disease, and they wanted to come and talk to me about their determination to try to spark more interest, more research, more focus on this disease.

Sadly, the life expectancy of those diagnosed is not long and they fear that many of the people who are the most passionate advocates will not be here long enough to fight the good fight and see good results.

What can you say to the couple and others that face this particular disease?

Dr. COLLINS. This is a particularly critical and heartbreaking condition, as you well know. We have redoubled our efforts to try to take advantage of some of the newer discoveries to come up with clinical applications. There is a consortium now called CReATe, which is Clinical Research in ALS and Related Disorders for Therapeutic Development.

We have been heartened by the success, which, I think I talked to this committee last year of a gene therapy for the infantile version of ALS called spinal muscular atrophy, which actually has worked quite well. And now the question is could that same approach be successful, at least for some individuals with ALS where we know what the genetic mutation is, and there are families where that is the case.

That is a big area of focus at the present time, but not the only one. So, we at least now have a consortium to put all the ideas that we can come up with into this space. It is a very hard problem, but I think our chances are better now than ever to make some real forward motion and maybe even some breakthroughs.

MATERNAL AND INFANT MORTALITY

Senator DURBIN. Thank you. My last point is this, as we are dazzled by your work and the breakthroughs in cystic fibrosis and other things, we also face the grim reality that this great Nation, this United States of America, maternal and infant mortality rates are absolutely unacceptable, particularly among some segments of our population. We cannot forget the basics here, and I know you are not, and I hope that you will be able to tell us—I have run out

of time now, but in some other context, the work that is being done in these two particular areas.

Dr. COLLINS. I would be glad to for the record, give you quite a summary of all the things that are happening there, particularly supported by National Institute of Child Health and Human Development which also covers maternal health. We agree that is a very high priority.

Senator BLUNT. Thank you, Senator Durbin.

Senator Moran.

PEDIATRIC CANCER

Senator MORAN. Thank you, Mr. Chairman. Dr. Collins, thank you and your colleagues for joining us today and for the work that you and your team across the country, do.

Let me start with Dr. Lowy. Doctor, the President has proposed a Pediatric Cancer Research Initiative, safer treatments for children, and better data.

What can you tell me about the challenges we face in fighting cancer among children, as compared to adults? Are there sufficient numbers of children who were willing to participate in clinical trials? What are the issues that are unique to childhood cancers?

Dr. LOWY. Thank you Senator Moran. One of the most important things to understand is that children who have cancer are not just small people who have adult cancer, but childhood cancer is qualitatively different. Whereas adult cancer has many mutations, often there are just are a few mutations that arise in children with cancer.

In addition, while there is a tremendous amount of interest in cancer treatment for adult cancer, there is less involvement in the private sector, so that NCI has a particular obligation to do research in this area, and we have substantially increased the amount of research that we do in this area over the last few years.

The particular proposal from the President is really along the lines of something that Senator Murray was asking about, which is how to efficiently and constructively aggregate data. And the goal as we envision it is to take pediatric cancer as an example, where some of the information is still quite siloed, and by aggregating it and pulling it together with an interoperable system, to be able to address important questions in pediatric cancer.

Fortunately, in the terms of participation in clinical trials, a high percentage of children with cancer participate in that and a lot of that is through the Children's Oncology Group sponsored by the National Cancer Institute, and because all childhood cancers are rare cancers this is actually an international effort that is part of the COG.

ALZHEIMER'S DISEASE

Senator MORAN. Thank you. Thank you very much.

Dr. Hodes, we have recently seen a number of late stage clinical trials focused on addressing Alzheimer's, that have shut down, highlighting the difficulty in achieving meaningful progress in combating Alzheimer's. What is your view on the current state of Alzheimer's research? Where is the future potential? And, maybe that is the questions.

Dr. HODES. Well, beginning with the failures in recent clinical trials, of course all of us are deeply disappointed at them, and these are efforts that are generally been targeted at amyloid protein individuals who already have symptoms. There are cases where there is very strong evidence to think that this amyloid pathway still may be important, in particular, in some of the early onset familial cases, but also by targeting earlier in disease, and so we are pursuing those specific areas.

But in addition, thanks very much to the increased funding that has come from Congress over past years, our understanding of the processes underlying Alzheimer's has improved enormously. Last year, for example, some 32 new genes were identified, more than had previously identified all around.

This has led to the ability to identify from those genes, bioinformatics, sys-biology, new targets. The number of targets is illustrated, Francis, we actually have a visual to look at. This is meant to show at stages from drug discovery, drug development, the phase one/two trials, the phase three trials, starting at the left the early stage of discovery, each of those bars represents a different kind of target currently under study. You can see the number of targets whether its inflammation or protein trafficking or proteostasis, that we are discovering more and more about as potential avenues.

So, the more targets we approach, the greater the probability and individuals with particular syndromes that we are going to have success. Out of some 35 clinical trials now ongoing, 13 are targeting amyloid, the rest have this multitude of targets.

So, a new generation of investigators, new science is leading us to this multitude of opportunities to make sure we have the way paved for a multitude of approaches to Alzheimer's disease.

NEXT GENERATION RESEARCHERS

Senator MORAN. Dr. Collins, the new set of scientists, the next generation, I cannot think of the young lady's name on your screen years ago, but you highlighted her as somebody we are going to lose because of the instability in research funding. And while I suppose we are always looking for the concrete evidence that the funds have resulted in a cure or a treatment, perhaps in the interim, between now and when we find all those cures and treatments, you can reassure me that the investment led by this subcommittee has made a difference in keeping, retaining, and encouraging young people to pursue careers in science and research.

Dr. COLLINS. I can, and I appreciate the question very much. Yes, that was a young woman as a graduate student at MIT who was about ready to give up.

That was a while ago and look at this curve which shows you our ability, thanks to you, to be able to ratchet up the awards that we have given to early stage investigators, that is people who have not previously been a principal investigator on an NIH grant. In 2013, that was a little less than 600, last year we challenged all the institutes to try to really push this forward and get us to 1100, we got to 1,287, by far the largest in history. We have made this a priority and every one of those individuals represents somebody with a lot

of energy, a lot of innovative ideas. This is the most important investment we could make.

Senator MORAN. Senator Shelby would have asked had he not run out of time, but on his behalf, I would ask if you would come to Kansas.

[Laughter.]

Senator BLUNT. Thanks Senator Moran.

Senator SHAHEEN.

Dr. COLLINS. I am going to be on a lot of airplanes here, I can tell.

[Laughter.]

Senator SHAHEEN. Well thank you, Chairman and Senator Murray for holding this important hearing, and thank you Dr. Collins and to all of you, for the amazing work that you do.

OPIOID EPIDEMIC

I want to begin with you Dr. Volkow, because as I know you are aware, we have a horrible epidemic in this country of substance misuse, and in New Hampshire we have been particularly hard-hit. I appreciate your coming up and meeting with some of the folks in New Hampshire who address this challenge.

Can you talk about what you are doing at NIDA (National Institute on Drug Abuse) that might give us some hope that there are additional medications, there are additional therapies on the way that might be able to help us address this epidemic?

Dr. VOLKOW. I think my microphone is not working, so can I borrow yours?

Indeed, this has become an area of priority area, and not just for NIDA but for the whole NIH and multiple institutes are working on it. And we have different strategies of research that are relevant to actually address a crisis.

With respect to medication development, for example, it has been a unique opportunity to bring in the expertise from the NCATS (National Center for Advancing Translational Sciences) Institute, the translational institutes, but also even from the expertise that comes from the NIAID Institute as it relates to that development of immunotherapies for addiction.

There are some exciting projects that are likely to bring us more rapidly alternatives like extended release formulation that improve the compliance of patients with their medications. We are also very interested in developing new tools that can be more effective in reversing overdoses that we are seeing, and people are reporting a higher dose of naloxone is needed to reverse overdose, when individuals are overdosing with drugs like fentanyl.

In the field of expanding access to treatment, we now know, and we do not need to do anymore research, that medications are extraordinarily effective in preventing relapse, and in preventing the overdosing, and in preventing infectious diseases, including hepatitis C, or in outcomes in Neonatal Abstinence Syndrome, but they are not being used.

The part of the problem is stigma, but another part of it is that we do not have sufficient infrastructure. So, we are working with researchers to develop models of care that they can advance the healthcare system, on the one side, and adjust the setting on the

other one. These two systems have been almost like different universes. So, we are using the funding that we are getting to bring them together and figure out how we can come with models of care that will treat the individual and sustain them in care.

And then a third.

Senator SHAHEEN. There has been an issue in New Hampshire, as you know.

Dr. VOLKOW. Yes, I know, and it is also a unique opportunity. We look at it in terms of preventing overdoses targeting both of them, as well as taking advantage, you just made me think, because New Hampshire has been incredible in terms of coming up with community solutions.

Senator SHAHEEN. Right.

Dr. VOLKOW. So, my perspective is how do we learn from those community solutions so that we can apply them to other States. We have an initiative called the HEALing Communities study that aims to do that.

And finally, an extremely important aspect that we have to keep in mind when we are addressing the crisis is research for prevention. And why is that so? Because if we do not prevent opioid use disorders, or we do not do interventions to prevent other addictions, we will be changing one for the other.

So, we have a very broad portfolio that covers these three different buckets.

Senator SHAHEEN. Thank you very much.

DIABETES RESEARCH

Dr. Rodgers, as you know, diabetes is one of the most expensive diseases in this country, and I was very disappointed to see that the President's budget actually called for a $280 million decrease in funding for NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases).

I wonder if you could—I do not think this committee will go along with that. I think we appreciate that investment in addressing diabetes research will help us in the long term to be more cost-effective, as well as to address the challenge that folks with diabetes face.

Can you talk about some of the breakthroughs that you are looking at now in terms of the artificial pancreas, which is really the most hopeful innovation to help folks with Type I, in particular?

Dr. RODGERS. Absolutely, thank you for the question. Yes, the FDA recently approved what have been truly breakthroughs for treatment of patients with type 1 diabetes, such as the first hybrid, artificial pancreas and the next generation of continuous glucose monitors that no longer require a finger stick for calibration, or that those are fully implantable.

I am happy to report that supported and the Special Diabetes Program have contributed to testing of all of these FDA approved therapies, and we continue to support cutting-edge research in this area. We are supporting advances in artificial pancreas in four very large, international clinical trials now, conducted at academic medical centers. Research using our special business funds is developing the next generation of management technologies.

The goal is to provide the patient and their healthcare provider with different options to decide what is the best artificial pancreas that could be used for that individual.

Senator SHAHEEN. Well, thank you very much. I am out of time, but I hope that our healthcare system and our health insurance companies will be willing to cover these kinds of innovations so people can actually benefit from them.

Dr. RODGERS. I agree.

Senator SHAHEEN. Thank you.

Senator BLUNT. Thank you Senator Shaheen.

Senator CAPITO.

Senator CAPITO. Thank you. Thank you, Mr. Chairman and thank you Dr. Collins and everybody for being here.

FUNDING NEW RESEARCHERS

The first question I was going to ask Dr. Collins, I think, has been asked a couple of times. We were really lucky to get Dr. Marie Bernard to come. Dr. Hodes was supposed to come but doing what he should be doing with his family, and one of the doctors in the room, researchers in the room expressed his concern about talented young scientists being frustrated with not being able to get into the queue.

So, you gave us the statistics of past had been 600, and now 1287, is that?

Dr. COLLINS. That is correct. That was for last year and we are going to aim to make a very good result this year. We are already starting to count these up and make sure that any investigator who scores in sort of, the top 25 percent as a first-time applicant, ought to have a very good chance, a very high chance of getting funded.

Senator CAPITO. Would you say those are geographically pretty much spread across the country then?

Dr. COLLINS. They are, as much as our grant portfolio is in general, and of course there are institutions that send more grants and others that send fewer, and the IDeA (Institutional Development Award) program helps us by balancing that.

Senator CAPITO. Right. Right. Thank you.

COORDINATING ALZHEIMER'S RESEARCH

Dr. Hodes, we did have a great visit and you were, as I said, well represented by Dr. Bernard.

One of the things that we talked about during the visit to West Virginia University was the work that is being done with the other institutes at NIH in conjunction with NIA, the National Institute of Aging, on different aspects of Alzheimer's. For instance, it was mentioned like a possible connection of low blood pressure and decreased cognitive impairment.

Can you talk about what kind of coordinating, you are doing at the Institute of Aging when you are looking and researching across the spectrum of NIH?

Dr. HODES. Thank you. It is a very important question and part of the success that we are going to have in addressing Alzheimer's disease, or other complex problems, of course, would be to recruit the best talent from a diverse area of science and expertise. So,

along the lines of previous conversation, over the past 4 years about one quarter of all of the awards have gone to new and early stage investigators. About one third have gone to new-to-the-field investigators who never even applied for research in Alzheimer's before, and last year a particular program, for example, invited grantees of all institutes whose research was not Alzheimer's directed, but who proposed a supplement to bring their creativity, their technology, their genius to the field to do so, and last year awarded some 300 supplements.

This we expect, and we are following up upon, will bring these people into the field. We directly fund the research on Alzheimer's and related dementias across all the institutes of NIH, so about $200 million last year actually supported awards to other institutes that are relevant to Alzheimer's and related dementias.

Senator CAPITO. Yes, I think that obviously brings an economy of scale a bit, but knocks down, I am sure like everybody else has, silos. I am sure NIH has had silos, not as many maybe.

Dr. COLLINS. Yes, past tense.

Senator CAPITO. Past tense. Yes.

Dr. COLLINS. We hope to knock them all down and we did pretty well, but we are still watching for them to try to come back.

Senator CAPITO. Right. Great.

NEONATAL ABSTINENCE SYNDROME BABIES

Dr. Volkow, as you know, my fellow Senator from New Hampshire, I know you have been to West Virginia. How many times now, two or? Three times and thank you for that visit; those visits that the NAS (neonatal abstinence syndrome) babies, Lily's Place and others, we do not know what the long-term effects of all of this is, I do not think. I think a lot of it may be in the science of the person's—as the child grows, their own health, but there are always external factors that are going to be impacting this, what kind of education, family life, etc. etc.

What are you doing with the NAS babies in terms of pharmacological research and specialized treatment strategies?

Dr. VOLKOW. Yes, and this is one of the priority areas for the HEAL initiative, to actually develop better treatment interventions that will improve the outcomes for the infants and that will lead us to understand better what are the consequences on the one hand, for a newborn that has during pregnancy their mother was taking opioids, but importantly, as they grow up in an environment where the mother may still be taking drugs and be subjected to a social deprivation.

So, on one hand one strategy is can we develop better treatments for Neonatal Abstinence Syndrome, and we typically treat them with, for example, morphine. Now, it is said that if you treat them with that small dose buprenorphine you significantly decrease the number of days that they actually have to be given the medication.

Just like we had also shown before that if you treat the mother with buprenorphine, as opposed to methadone, you decrease almost by half the number of days that you actually—the infant that is born out of that mother will have with her withdrawal symptoms.

We are also funding research, and again, this is in partnerships with other institutes, including the National Institute of Child

Health and Human Development about non drug interventions, and this has emerged out of root grass of communities that have had to deal with the problem. And, for example there is recognition now that physical contact of the infant with the mother, could actually decrease the amount of morphine that is necessary to control withdrawal. So, we are funding research to develop the evidence about what are the optimal interventions.

And finally, as it relates to your question about what is going to happen with these children. There has been already some research that shows that in infants that are born out of mothers who were exposed to opiates, if you provide a supportive environment those children grow up to not have evidence of cognitive impairments.

But we are actually in the planning phases of launching a very, very large study that will follow close to 8,000 infants as they go from infancy to adolescence to evaluate how exposure to drugs influences brain development trajectories.

Senator CAPITO. Yes, I mean that sounds very powerful and the troubling part is, it has to be a long-term study to be able to see the effect and by that time, the effect has taken hold.

Thank you so much for your good work. Thank you.

Senator BLUNT. Thank you Senator Capito.

Senator Lankford.

Senator LANKFORD. Thank you, Mr. Chairman. Thank you all.

A quick story. I was sitting on an airplane about 3 months ago, sitting next to a gentleman flying back to Oklahoma. He leaned over, introduced himself as a fellow Oklahoman and we chit chatted for a while, and I said, what brings you to Washington? He said, "I come often. I am in an NIH trial, and I have been for years" and he smiled, and he said, "And, I am still here."

And from watching his smile and chit-chatting with him on the two-hour flight back home, it reminded me again of how many people that are still around, just like he said, because of the work that you are doing.

So, thanks for continuing that work and for helping folks that, literally for him, as you know, he had been through everything to be able to get to your desk, to be able to get to that spot. So, we appreciate it very much.

BRAIN MAPPING

Dr. Collins give me an update on the brain mapping. I want to walk through several things we talked about in the past. We have obviously made significant investments into that. I missed the very opening statement of this in a previous thing that I had to be able to get to as well this morning. Tell me where we are on brain mapping.

Dr. COLLINS. I would love to talk about this. This project, which began 4 years ago has very ambitious goals to really understand, what are the cell types in the brain? There are 86 billion of those cells, so that is a pretty big challenge. And how are they connected together and how do the circuits in the brain do the amazing things that they are capable of, and how can that go awry and result in disorders like Parkinson's disease or epilepsy, or a long list of others?

We, after 4 years, I would say have met or exceeded every one of the milestones that was put in place when the original plan for the 10-year program was put forward.

So, you are asking the question at an appropriate moment. Right now, we are having a meeting of all the brain investigators at the Marriott at Wardman Park, and this evening I will chair a panel that will look at the plan now that is being revised, we can call it brain 2.0, of what we might be able to accomplish given the platform that has already been built.

It is exciting from what we have already learned in terms of new principles about how brain actually does what it does. It is exciting by the people that have come into it, and the latest couple of rounds of grant awards, more than half of them were engineers, who would not necessarily be coming to NIH with grant applications, but they are fired up about this too. And that interdisciplinary part of this is part of the reason that I think it is turning out to be so successful.

Senator LANKFORD. Okay, thank you. Well, we will want to get a detailed update because we want to make sure it stays on track, obviously, but this is a massive project, as you detailed before.

Dr. COLLINS. Yes.

NONADDICTIVE PAIN TREATMENT

Senator LANKFORD. You have brought together folks from the outside and from private companies to be able to talk about alternatives to opioids and developing a nonaddictive pain treatment.

How are the outside groups, private entities, pharmaceutical companies, cooperating with you? Is that group still together, still working?

Dr. COLLINS. Actually, quite well. We have in fact, put in place a combination of scientific expertise from academia from NIH and from industry, and we are now trying to prioritize what may be, is many as 60 or 70 possible therapeutics that would be nonaddictive treatment for pain, but which have been slowly moving through the pipeline.

We at NIH are setting up a clinical trial network for people with chronic pain syndromes so that these can be tried out in a rigorous way, and companies are willing to contribute those.

Senator LANKFORD. They are staying engaged?

Dr. COLLINS. They are staying engaged.

Senator LANKFORD. Okay, that was the risk at the beginning, to say you are bringing together competitor groups to be able to say we have got to sit down and solve this right now, together, so.

Dr. COLLINS. Yes, I met with the 20 pharmaceutical companies that have the largest budgets last weekend and they were all on board.

DUPLICATIVE RESEARCH

Senator LANKFORD. Okay, thank you. Let me read a GAO report real quick and I want to be able to get a follow-up from you.

Their statement was, they talked about VA, CDC, NSF (National Science Foundation), DoD, NIH and they said, "Each lack a comprehensive information on health research funded by the other

agencies, which limits their ability to identify potential areas of duplication in the health research they fund."

They made that comment just looking at the broad picture of all of the research that is happening in multiple different areas, the Appropriations Committee appropriates.

How is it working to be able to cooperate with VA, DoD, especially large programs, NSF, to make sure, because as you would know, grant folks are requesting of everybody. So, they will have a slightly different name for similar research and go to as many institutions as they can to be able to see if they cannot find money to do the research on it.

How are we doing being able to avoid the duplication and communication on agencies?

Dr. COLLINS. Senator it is a great question and it is something we are quite invested in. We have a whole office of portfolio analysis that has now been working at coming up with tools to allow us to look, very complicated research portfolios what are the areas of overlap?

We have done that kind of analysis comparing NIH to NSF, comparing NIH to the DoD programs, comparing NIH to ARC. It is very informative to be able to see that in a visual form, and we have in few instances identified places where there was duplication and acted upon it.

We have not yet done this as much for VA, but that is next on the agenda. As long as we have access to the abstracts for the grants that are being funded, we can do this right away.

Senator LANKFORD. You are breaking down silos at NIH. The challenge is going to be for us to break down silos in medical research across multiple agencies to make sure researchers can meet with each other, and we know we've got similar research and we are sharing that information, and we are not duplicating it.

I will have a question for the record that I will follow up with you, I know you had an interchange with Representative Harris on fetal tissue research. HHS is in the process of doing a review of all fetal tissue right now and I know there is somewhat of a pause going on as they are waiting for that to be responded on, but I will do some follow up with some questions for the record with you on that as well.

Dr. COLLINS. I will be glad to answer for the record.

Senator LANKFORD. Thank you.

Senator BLUNT. Thank you, Senator Lankford. We will probably have a chance for a second round, if you want to stay.

Senator Baldwin.

Senator BALDWIN. Thank you, Mr. Chairman.

NEXT GENERATION RESEARCHERS INITIATIVE

Dr. Collins, you and I share a passion on a personal priority of investing in our Nation's next-generation of researchers. I think most everyone on the subcommittee knows from my retelling the story that I was raised by my grandparents, and my grandfather was an NIH-funded scientist, a biochemist. So, I grew up understanding the importance of the contributions of our researchers to biomedical leadership.

In 2013, I had a particularly powerful meeting with a high school student. He was a bone cancer survivor from Fond du Lac, Wisconsin, and his name is Ian and Ian told me that cancer research helped save his life. He decided at that point that he wanted to grow up to be a scientist and to help others who had the disease. But he was concerned that it would not be possible for him to break in as a new researcher due to NIH funding cuts.

Ian inspired me to author the Next Generation Researchers Act with my colleague, Susan Collins, to improve NIH opportunities for our new and early-stage researchers.

I am proud to report to you that Ian has graduated from college and is now working in a lab with a scientist at Huntsman Cancer Institute in Salt Lake City, Utah studying pediatric cancers like osteosarcoma.

I applaud NIH's progress in implementing my Next-Generation Research's Initiative to help support future scientific leaders like Ian. In fact, as you noted, NIH funded 1287 early-stage investigators in 2018, as part of this work, the largest number in history.

I would love it if you could elaborate on NIH's work to implement this initiative since it was signed into law back in 2016, and your plans for implementing it moving forward, and any comments you might have about the National Academies Consensus Study Report on the Next Generation of Biomedical and Behavioral Sciences researchers.

Dr. COLLINS. Well Senator, I really appreciate the way you have drawn attention to this critical issue, and we have named our initiative the Next Generation Researchers Initiative after what you authored, because we were totally in sync with this as one of our highest priorities.

When Ian asked you the question how we were funding, according to the graph here if it was 2013, less than 600 early-stage investigators, and that was a time where it was challenging for somebody trying to get their career started to have confidence that there was going to be a path forward.

And notice what has happened since then, thanks to the strong support of this committee, and to our prioritizing early-stage investigators as the most important applicants that we see, and yes, we are now in 2018, up to 1287. We aim to try to keep a level in that space going forward. I think that is a pretty healthy number. This is not one of those where we want to go up and then go back down again, because there is plenty of remarkable talent out there.

So, in addition to, of course, trying to be sure that we are doing this in a fashion that attracts really talented people, we also are focused on diversity. We want to have more women in this category, because we still have not achieved the point where our grantee pool is what it could be, given that PhD's now are being granted 50–50 to men and women, yet we still as first-time applicants to NIH, it is about 30 percent that are women.

We are coming up with ways to try to make this pathway seem more appealing, and for us to be more welcoming, and of course that means dealing with the sexual harassment issues that Senator Murray rightly brought up earlier.

We did support that report from the National Academy and we have strong agreement with many of its recommendations in terms

of what we need to be doing to sustain this, but as I briefly said earlier, I am perceiving, and Ian is a great example, of a good deal of the change in the enthusiasm and excitement out there in institutions of young graduate students, postdocs, junior faculty really see, okay this is a good time to be in science, not a time where we have to worry about our future quite as much as we did 5 or 6 years ago. So, thank you for the way you have supported this.

Senator BALDWIN. Well, thank you.

I have been concerned that President Trump's budget would cut NIH funding by over $4 billion, as years of budget cuts are one of the primary factors in discouraging historically, young scientists from getting into the field or forcing them to leave the field to pursue careers in other countries or in other realms. Yet, no investment in my mind promises greater returns for America than our investment in biomedical research.

Will the Next Generation Researchers Initiative deliver on its promise and be able to continue to hit such ambitious milestones as you are describing, under the administration's proposal to reduce overall funding for the NIH?

Dr. COLLINS. Well of course, everything we do depends on the overall support that we have available. This Congress, and this particular subcommittee has been very attentive to that and the opportunities that we have had over these 4 years of seeing our budgets go up by a total of 30 percent, have made a lot of these things possible.

We always though, have to adjust based upon the resources that we have. I will tell you of the institutes at this table and the others who are not here, this funding of early-stage investigators is one of our highest priorities. We will seek to make that happen to the level that we can with the resources we've got.

Senator BALDWIN. Thank you and Chairman Blunt and Ranking Member Murray, I oppose the President's budget request to slash funding for NIH, and I look forward to working with both of you to increase funding both for NIH and for a special focus on the Next Generation Researchers Initiative in the fiscal year 2020 budget.

Senator BLUNT. Well thank you, Senator Baldwin.

Senator ALEXANDER.

Senator ALEXANDER. Thank you, Mr. Chairman. Dr. Collins and your team welcome.

First I want to once again salute Chairman Blunt and Senator Murray, and others who have worked over the last 4 years for such steady progress in funding for the National Institutes of Health. One reason we have done that is because we had such great confidence in your leadership and that of your team that you would spend the money well. So, it is a testimony to you and very important.

OTHER TRANSACTIONAL AUTHORITY

In the opioid's legislation, we did something that you had asked us to do when we talked about 21st century cures. That was to give you other transactional authority so you could deal with such things as a nonaddictive pain medicine.

The committee that Senator Murray and I are ranking on, we recently had a hearing on pain and that exacerbated— that reminded us that when we limit the supply of the most effective pain medicine, opioids, to millions of Americans, that causes a lot of worry among people who live with pain every day, and there are millions of them.

So, my question is, what have you been able to do with the other transactional authority that we gave you to help find new nonaddictive painkillers?

Dr. COLLINS. It was very helpful, in fact essential, to have that kind of authority to move quickly in this space of putting together an unprecedented public/private partnership to try to speed up the development of those nonaddictive pain medicines.

As I mentioned a couple minutes ago, we are working now with pharmaceutical companies who were willing to put forward compounds, we are calling them assets, but basically, they are untested drug compounds that are ready for clinical trials but have been slow moving through that pipeline.

We then need to do a very quick review of how to prioritize these, we cannot test 60 of them, but we might be able to ultimately run trials on a dozen or so. Which means we need to have a process of review that is very streamlined, and it needs to be supported in a way that would be very hard to do with a traditional grant mechanism.

The other transaction authority is exactly the tool that we have needed in that space; it has been essential, and so we are grateful for it.

Senator ALEXANDER. Good. Well, there is—I have an even higher sense of urgency about the nonaddictive pain medicine and treatment and accelerating our effort for that.

Let me go back to April 2016, you testified before this subcommittee and made 10 bold predictions of what might be able to happen in the world of medical miracles over the next several years. A lot of them are happening, and you have mentioned them today. Are you ready to update your 10 bold predictions for the next 10 years?

[Laughter.]

Dr. COLLINS. I probably could do that. It would be kind of fun because there were some things that I do not think I put down in 2016 that I could now be pretty enthusiastic about. So, for instance, in 2016, I do not think I would have been bold enough to say that we would be curing sickle cell disease, and yet we are now seeing in at least three clinical trials that NIH is supporting, examples of individuals who are cured.

Senator ALEXANDER. Is that because of CRISPR?

Dr. COLLINS. That is, CRISPR is in there, and other kinds of gene therapy making this possible. Some of the things we put down at that point, I thought were a bit overly optimistic, and yet maybe I underestimated how quickly things would go. We earlier talked about the artificial pancreas and, you know, I put that one down and a year later FDA approved the first one.

REGENERATIVE MEDICINE

Senator ALEXANDER. That is pretty common, right.

Well, what about regenerative medicine? The juvenile diabetes folks say that the next step is regenerative medicine might help actually change the cells so you would not have to use the device. Is that possible?

Dr. COLLINS. I think that is the ultimate goal. Maybe Dr. Rodgers would like to make a quick comment, to go from what is currently a technology that is like a servo mechanism with some nonhuman materials, into a human version of an artificial pancreas derived from stem cells.

Senator ALEXANDER. But the impact of that would be astonishing, wouldn't it?

Dr. COLLINS. Profound, and it would be your own cells so this would not be a transplant, it is basically——

Senator ALEXANDER. So, you would not have to prick for your blood every day?

How would that work Dr. Rodgers?

Dr. RODGERS. Well, that is a great question. Cell replacement therapy is certainly an area that we are also, in addition to the artificial pancreas technology looking for a curative therapy. The goal here would be to stimulate the person's own beta cells, those cells that are lost due to autoimmune disease, and get them to replicate to expand them. Or alternatively, use of the remaining cells, such as the alpha cells that make glucagon, and trick them into actually becoming beta cells so that insulin can then be produced as well.

One thing that we are doing in that space, using these islets, the cells that make insulin, is actually putting them on a chip. I have actually brought a copy of one to illustrate for the committee. These islet cells are put on this chip together with cells that replicate the pancreas environment blood vessels, as well as components of the immune system. In that, you can mimic the disease on a chip.

The potential of this is that we may be able to test therapies in advance and save some of the expense and time associated with testing novel technologies in humans and get those that are likely to fail out of the way. So, we really have a lot of enthusiasm about this type of work.

Senator ALEXANDER. Thank you. My time is up.

But I look forward to you updating your bold predictions, Dr. Collins.

Dr. COLLINS. You are on.

Senator BLUNT. Alright. We will look forward to the list of bold predictions.

Dr. Fauci, I am going to take 5 minutes here, and I have three questions and maybe we can deal with all of them in 5 minutes. One, is measles. What do you think is happening and how concerned we should be about it?

Two, the antibiotic resistance, the fungus that we are having problems, big problems in a couple places in the country now. Then, three would be the President's HIV 10-year prediction to not have transmission, or not have this as a problem anymore.

So, start with measles.

MEASLES

Dr. FAUCI. Thank you, Mr. Chairman. Measles is really a formidable problem that is growing. It is a completely avoidable problem, which is the reason why we in the scientific and public health field are so frustrated by it.

If you look at the year 2000, we here in the United States had essentially eliminated measles. By elimination, it means that there are no transmissible cases in the country over a 12-month period. Yet over the last several years there has been increasing numbers of cases of measles, and I will explain in a moment why that is occurring.

The problem right now, this past 3 months of 2019, we have had 465 cases of measles in the United States, which is more than we saw all of last year. And the cause of that is very clear, it is individuals in the community who are not vaccinating their children, leaving a vulnerable group such that when someone comes in from the outside, from another country where measles might be rampant and into the community, that if you have that veil of protection that you need when you need a certain critical percentage of the population is vaccinated, and for measles that means between 93 and 95 percent.

But look at what is going on now, in the State of Washington, in the Rockland County, New York and very, very importantly, in the middle of New York City in the Williamsburg section, where the Hasidic Jewish community goes down to around 70 percent protection, which means that veil of community immunity is gone.

That is the reason why we are having this outbreak. It is very frustrating, because measles is one of the most transmissible viruses known to man and we have a vaccine against measles, which is one of the most effective vaccines known to man, and yet those two are not coming together with this hesitancy to get vaccinated.

So, our goal and our purpose now, is to try and educate people to understand the importance of not only protecting their own children but protecting the community. That is measles.

CANDIDA AURIS FUNGUS

The fungus that you alluded to; it is called Candida auris. Fungi in general that we see are mostly, I would not say benign, but relatively easily treatable. The problem with this fungus that is now come out about 500 or so cases, is that we are seeing in hospitals particularly, a fungus that is rather resistant, if not completely resistant to the antifungal agents.

This is particularly important for individuals who are immunosuppressed, people on cancer chemotherapy, or people who have underlying immunosuppression. You have read about it in the front page of the New York Times, but this is becoming a problem that we have to address, and it falls under the big umbrella of the antimicrobial resistance.

HIV

Third, the President's announcement at the February 7th State of the Union Address about ending the HIV epidemic as we know it in the United States, and this is based on something that has

happened for many years largely supported by this committee, is the development of the tools to do just that.

We have drugs right now as you well know, I have spoken to you about this, that if you treated an individual who is HIV infected and bring down the level of virus to below detectable level, not only do you save that person's life but you make it essentially impossible for that person to transmit the virus to someone else.

And then there is preexposure prophylaxis or PREP, which means that if you are at high risk of getting infected and you take one pill a day, you can decrease by 97 percent the likelihood that you actually will acquire infection.

You put those two things together and you look at the map of the United States, why it is so unique. We have 3,007 counties in the United States, in 48 of those counties, plus the Washington District of Columbia, plus San Juan, more than 50 percent of all the infections in the United States come from that very restricted group.

So, the plan is to take this demographically and geographically concentrated area, and as I say, put a full court press on getting into the community and implementing each of those.

So, I will stop there, and I give you back 10 seconds.

[Laughter.]

Senator BLUNT. Well, that is back to the observation earlier that you have testified before, you have three questions, exactly have timed them out and land on time.

Senator Murray.

SEXUAL HARASSMENT

Senator MURRAY. Thank you very much and Dr. Collins I know you are aware of a recent study in the Journal of American Medical Association, which found the gender differences, you talked a minute ago about that, in the amount of NIH funds awarded to first time female, and male principal investigators that favored men receiving larger grants than women. And data shows that in academic medicine, which for years has trained just as many women as men, the percentage of women in the workforce decreases at every career stage, such that women make up only 25 percent of the professorate.

And your conversation with Senator Baldwin indicates you are aware of a study that also found that women held fewer grants, submitted fewer applications, and were less successful at renewing grants than their male counterparts.

So, in light of the National Academy's report last summer, which showed that sexual harassment is rampant in academic science and undermines women's professional attainment, in some cases, leaving women to leave the scientific workforce entirely, the cumulative effect results in significant damage to research integrity and a considerable loss of talent in our country.

So aside from its economic and potential scientific impact that loss of talent actually represents a significant cost to our taxpayers. It has been estimated that each newly minted Ph.D. costs $500,000, and of course it is a personal loss to women who feel pushed out of the field they love.

So, given all that, can you comment on actions that NIH is taking to address this attrition of women from the biomedical workforce?

Dr. COLLINS. I would be happy to. This is a very critical issue and there are multiple factors, but certainly the realization of how prominent and pervasive sexual harassment has been leads us to push even harder to address this issue. It is unacceptable, it is morally indefensible, and it drives talented women away from the workforce who could make wonderful contributions.

If you look at this graph, it sort of shows you what has happened as far as the percent of various types of grants that are going to women. You can see in the career awards, which are generally people early in their independent phase we are doing better over time, we are actually doing better with research project grants, but the curve is way too slow in terms of its upward movement. That ought to be 50 percent, and it is not that there is a discrimination against women who apply for grants, if you look at the likelihood of getting funded, men versus women, it is almost exactly the same. The problem is we are not getting the applications.

Senator MURRAY. They do not apply.

Dr. COLLINS. And that is clearly an indication that there is something about our environment that is not welcoming, it does not feel like to many women, a place they really want to be. There are lots of factors in there in addition to the sexual harassment issue, there are family issues, and there are the issues about who has responsibilities for other parts of the community that people are coming out of. There is this sort of concern that if you look around, where are the mentors.

I believe we really need, not just to try to address the things that are the most egregious as far as the sexual harassment, but also the gender harassment. The way in which our culture encourages women, often times to think they do not belong there by subtle comments that are made, usually by men. We have to change that, the best way to change that is to get more women into leadership positions.

Senator MURRAY. I am looking at your panel, it's great, but——

[Laughter.]

Dr. COLLINS. Well, yes, look at our panel, just take a snapshot here, this is a good example of what we need to change.

We are actually looking at our intramural program right now to try to see, are we doing enough there to provide opportunities for talented women to rise through the ranks or are we too ossified by people who get into a position and stay there too long.

We are taking this with great seriousness. I grant you, we should have done so sooner, and I am apologetic to those who think we have not done enough. We are determined to do better.

Senator MURRAY. Okay, I appreciate that. Thank you very much and of course, we all have to participate, and appreciate your taking this seriously, look forward to working with you on it. I think we are losing talent from an early age and it gets worse as we go on. We have to make sure we have all of our talent at the table. So, thank you.

Dr. COLLINS. I agree with you.

METHAMPHETAMINE DEPENDENCE

Senator MURRAY. Dr. Volkow, my last question. There is a lot of hope in my home State that opioid-related overdoses may have peaked, but we have been seeing an alarming increase in methamphetamine overdoses now, and as you know there is no FDA approved treatments for methamphetamine dependence.

Can you tell me what NIDA's efforts to development treatment for methamphetamine addiction is right now?

Dr. VOLKOW. Well, you are asking me a question that actually literally makes me extraordinarily anxious and keeps me awake at night, because we are seeing the numbers of mortality increasing for methamphetamine and cocaine too, and even though we funded research to come up with treatments none of them have reached the outcomes that are actually necessary to get them approved and show them effective.

However, what is very exciting in the whole area and possibility, relates to immunotherapies, and in fact, where we have done the greatest advance is developing monoclonal antibodies for capturing the drug so that the drug gets sequestered in the blood and never gets into the brain obviating any pharmacological effects, happens to be for its application on methamphetamine.

So, we have brought those antibodies already into humans, and what we are trying to work right now is the extent to, which by partnering with some of the scientists who are part of the NIAID Institute and the Cancer Institute, on developing longer lived, the monoclonal antibodies extent to which we could apply them. Because they work, they capture it, the problem is they are not long-lasting, so you have to repeatedly immunize.

So, this is one of our priorities as it relates to medications.

In parallel of course, we are funding research in terms of behavioral interventions to try to actually improve the outcomes on individuals that are suffering from methamphetamine addiction.

Senator MURRAY. Okay. Thank you very much, I really appreciate it. And thank you to all of you for being here today. I appreciate the great work you do.

Senator BLUNT. I have just a couple of more things as we finish up here.

YOUNG RESEARCHERS

Dr. Lorsch, we talked about young researchers. I think you have also been experimenting with longer research times for grants. Would you talk about that and talk about whether there is any impact that your appropriation stream has on being able to do that?

Dr. LORSCH. Thank you very much, Senator. We have developed a new program called Maximizing Investigators Research Awards, or MIRA, which has several goals, but one as you said, is to give a longer and more stable funding stream to investigators. We hope that by doing that, and by also giving them more freedom to basically follow their noses as their research evolves, we will allow them to do more ambitious research and to get faster to discoveries through this process.

There are two parts of it; one is the established investigator part, and the other is the early-stage investigator part.

The early-stage investigator part is actually particularly exciting right now because since the program started in 2016, we have seen a doubling of the number of early-stage investigators that we fund at the Institute, primarily through the MIRA program. We have seen a 60 percent increase in the number of applications from early-stage investigators. So, they are clearly speaking with their feet that this is the way they want to see science supported.

And what is particularly exciting is we are actually funding them at a younger age, so all 3 years of the program, the median age of funding for early-stage investigators in MIRA is 37, whereas it is 38 for early-stage investigators funded through RO1s and we are hoping that trend is going to continue.

What I will say for the record, is that one of my strategic goals for the Institute is to try to push that age of funding for MIRA down to 35. I think 37 is still too late to be getting your first grant award.

Senator BLUNT. Well, thank you for that.

NON-ADDICTIVE PAIN MEDICATION

Dr. Volkow, you know we have had a 30 percent increase in NIH and we are all pleased about, and during that same period of time we have had a 1300 percent increase in money going to the opioid fight.

I do not know that we have talked yet today about alternative research to have pain medicine that is not addictive. Do you have any more you want to add to that?

Dr. VOLKOW. There are two components to it, one of them is in terms of the basic science that Francis was speaking of that allowed us to identify completely novel treatment targets, molecules or immunotherapies for management of pain.

And then those interventions that do not rely on biologics or medicine, and that includes behavioral interventions to evaluate the extent that they can improve the outcomes, as well as an area that is very exciting in the whole area of brain diseases, is the use of neuromodulation technologies like magnetic resonance, transcranial magnetic resonance stimulation, or direct electrical stimulation, to modify certain areas of the brain, in means to improve outcomes.

The research, for example, there are several papers that have shown positive effects for various chronic pain conditions that offers an opportunity. There is also, as part of the HEAL initiative, a project that is going to be evaluating comprehensive models of care, just as the CDC recommends for the management of chronic pain, that will determine the extent for which they are effective and optimize our understanding about what are the active ingredients and how to sustain them. And too, at the end recognize that chronic pain is an extraordinary, difficult condition to treat, and that it is terrigenous and that we may require to do what is done in cancer, personalize intervention.

So, doing that research that will enable us to get there will be very important in helping patients suffering from severe chronic pain conditions.

Dr. COLLINS. I just want to weigh in for a minute here and say how incredibly helpful it was for the Congress to identify this as

an area, both of great need and of great opportunity, and the $500 million that you put into the budget beginning in fiscal year 2018 has made it possible for us to solicit truly bold ideas across all of NIH.

We now have 20 of our institutes engaged in this, more than 40 different funding opportunity announcements, some of which have already received grants, have been reviewed and are starting to be funded; some of which are still out there for solicitations. By the end of this fiscal year we will have put the largest infusion of research into finding nonaddictive alternatives for pain that has ever happened at NIH, in addition to funding a very large amount of efforts to try to help how to manage opioid use addiction, which is obviously our National crisis.

We could not have done this at this scale without your help, and it has made all the difference.

SEPSIS

Senator BLUNT. Good. I do not remember the first time I noticed that somebody's cause of death was sepsis. It does not seem to me it was that long ago, but it does seem to me that I see that often now.

What are we trying to do there, and is that an NIH issue that you are dealing with?

Dr. COLLINS. It is. Maybe I will ask Dr. Lorsch to say a little bit about the basic science part, and Dr. Fauci about the clinical efforts, because those are hand in hand.

Dr. LORSCH. Thank you very much. Sepsis research is supported jointly by three main institutes, one is NIGMS, one is Dr. Fauci's Institute, NIAID, each of which fund about a third of sepsis research, and Heart, Lung, and Blood funds about a quarter of it and the remainder is Child Health and Dr. Rodger's institute.

I became concerned a couple of years ago that the pace of research in the basic part of sepsis understand the mechanisms underlying the condition was not fast enough. So I put together a working group of our advisory council, which right now is examining our portfolio and the field and how it fits in with the rest of what NIH is funding, and they will be making recommendations to us at the May council meeting that we will have next month.

Particularly they are going to be looking at the balance of research in animal models versus in humans. We are concerned that perhaps there is too much emphasis on looking at sepsis-like conditions in mice and not enough in actual human condition. And we are also looking at ways we can leverage clinical trials networks that are funded by other institutes that are already enrolling critically ill patients who may develop sepsis.

And perhaps, Dr. Fauci wants to say a little bit about that.

Dr. FAUCI. Thank you, Mr. Chairman. The effort against sepsis as Dr. Lorsch has mentioned, is really multifaceted, because you have a micro-organism, a pathogen that triggers a process that is a physiologic and pathological process that leads to what we now know as sepsis. It is not just the microbe and it is not just the response; it is a combination of the two.

NIAD's role is to study specifically the microbe itself, the virilism of the microbe, the processes that trigger these physiological and patho-physiological events, as well as treatment.

And as Dr. Lorsch mentioned, we have a clinical trials network that we look at these patients, it is very difficult to actually study them, because when they come in it is such an acute situation that you have to move very quickly when you are doing a clinical trial. But we are working with other institutes, including the National Heart, Lung and Blood Institute, to do this kind of synergy of multiple approaches to what is a very complex and heterogeneous problem.

Senator BLUNT. Well, Senator Murray, we are about to finish here, is there anything that we should have asked that we did not ask Dr. Collins?

Dr. COLLINS. You did a pretty fine job of covering a lot of the landscape with the folks who are here. And again, I have to say how much it has impressed me over the years about how much the members of this subcommittee have become so deeply knowledgeable about what we do.

These conversations always end up being full of really rich details and digging into areas that we love to talk about. So, many thanks to you for all of the ways in which you have spent your time on these issues, and of course, we would love to invite you back out to NIH any time because we always have new things to show you.

ADDITIONAL COMMITTEE QUESTIONS

Senator BLUNT. All right. The record will stay open for one week for additional questions.

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

QUESTIONS SUBMITTED TO FRANCIS S. COLLINS, M.D. PH.D.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

CHINA'S THOUSAND TALENTS PROGRAM

Question. I'm very concerned that the NIH research community is not being adequately informed of the threats they are facing from foreign government programs specifically designed to undermine U.S. research. What specific steps are being taken to: (1) better inform the research community of the specific threat; (2) ensure there is disclosure of foreign collaborations and affiliations; and (3) implement controls to protect the integrity of the peer review system?

Answer. NIH shares your concern about foreign government programs that are designed to undermine U.S. research. NIH is committed to working with other agencies and offices, including law enforcement, as well as with the extramural community, to identify and confront the risks these programs pose and to combat them. As described further below, NIH is employing a multi-pronged approach addressing individual situations and developing proactive programs to address these threats.

Informing the Research Community

NIH's efforts to inform and engage the research community are proceeding across multiple platforms. For example, multiple communications to the research community over the last several years have focused on the imperative that applicants and recipients inform NIH of foreign support, and the obligations and certifications of reviewers to protect the confidentiality of grant applications, study section deliberations, preliminary scoring and reviews. For example, an NIH Guide Notice [1] issued

[1] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-160.html.

in March 2018 reminded applicants and recipients of the requirement to disclose to their institution significant financial interests, which can include support coming from foreign governments or other foreign entities; the institution determines financial conflicts of interest that must be reported to NIH and managed on an ongoing basis by the institution. On August 23, 2018, the NIH Director took the unusual action of issuing a comprehensive statement on protecting the integrity of U.S. Biomedical Research. The Director also took the unprecedented step of issuing a letter to officials at approximately 10,000 recipient institutions. This letter informed the research community that the agency is aware that some foreign entities have mounted systematic programs to influence NIH researchers and peer reviewers, as well as to take advantage of the long tradition of trust, fairness, and excellence of NIH supported research activities. Furthermore, NIH convened a working group of the Advisory Committee to the NIH Director on Foreign Influences on Research Integrity. This panel was comprised of leaders in higher education, members of the extramural community, and experts in security, and was charged with assisting the Advisory Committee in making recommendations to the agency, which are currently being implemented.

In order to address specific cases brought to the attention of the agency, NIH has contacted nearly sixty institutions regarding concerns about scientists who may have failed to disclose foreign affiliations or significant financial interests stemming from foreign-based entities or governments. This approach has proven highly effective in both communicating concerns to the extramural research community, engendering partnerships to develop best practices, and gaining compliance with Federal and NIH grants requirements and policies. NIH's efforts have been widely reported within the science and popular press, e.g., by the Houston Chronicle,[2] Science Magazine,[3] and The Cancer Letter,[4] which is expanding our impact. We are actively engaging the research community and in turn, they are actively partnering with us. For example, Penn State University,[5] M.D. Anderson,[6] and the University of California San Diego[7] have posted new guidelines for faculty. Professional societies such as the American Society for Biochemistry and Molecular Biology[8] are acting to share our concerns across the research community. We appreciate all the members of the research community who proactively work with us to address these matters.

Furthermore, NIH regularly communicates with grantees to provide training and compliance support for issues involving conflict of interest requirements at NIH-led conferences such as the NIH Regional Seminars. This information is also communicated by NIH through professional organizations such as the Federal Demonstration Partnership, Society for Research Administrators, American Association of Universities, Council on Governmental Relations, Association of Public & Land Grant Universities, and the National Council of University Research Administrators. There have been a number of special meetings involving these groups and others to address the recent concerns on foreign influence. In addition, NIH recently developed an online training module on Financial Conflict of Interest as a resource for both NIH staff and the extramural community. NIH's outreach and engagement have facilitated extensive faculty outreach at research organizations as well as led to developing and sharing best practices.

Moving forward, as Dr. Collins said during the Senate Appropriation hearing, "We will not rest until we've looked at every possible example. We have to depend on the universities as our partners in this, but we are driving this process as vigorously as we can." Additional institutions will be contacted when new discoveries are made. NIH will continue to remind the extramural research community of the need to be transparent regarding other support, financial conflicts of interest and foreign components, to better address research threats.

Finally, NIH is actively partnering with other Federal departments and agencies to address concerns related to undue foreign influence on the biomedical research enterprise. These Federal partners include the Central Intelligence Agency, Federal

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[2] https://www.houstonchronicle.com/news/houston-texas/houston/article/MD-Anderson-fires-3-scientists-over-concerns-13780570.php.

[3] https://www.sciencemag.org/news/2019/04/universities-will-soon-announce-action-against-scientists-who-broke-nih-rules-agency.

[4] https://cancerletter.com/articles/20190426__3/.

[5] https://www.research.psu.edu/international__affiliations.

[6] https://www.mdanderson.org/newsroom/md-anderson-addresses-national-threat-of-foreign-influence-.h00-159302256.html.

[7] https://medschool.ucsd.edu/vchs/research-services/hssppo/review/Pages/Foreign-Involvement-.aspx.

[8] http://policy.asbmb.org/2019/01/02/updates-from-the-nih-advisory-committee-to-the-directors-december-meeting/.

Bureau of Investigation, HHS Office of Inspector General, Department of Defense, Department of State, and the National Science Foundation.

Ensuring Disclosure of Foreign Collaborations and Affiliations

NIH requires institutions, as the applicants for and recipients of NIH funding, to ensure that individual investigators make all appropriate disclosures to their institution regarding other support, affiliations, and financial interests, whether or not they are employees of the institution. Institutions, in turn, must ensure that all applications and reports submitted to NIH are complete and accurate.

Prior to making an award, NIH requests and reviews updated "other support" information for the program director/principal investigator and other key personnel identified in the grant application to ensure that updated information on all financial resources, whether Federal or non-Federal, foreign, commercial or institutional, available in direct support of an individual's research endeavors, are known and considered prior to award. This includes foreign financial support. NIH uses this information to ensure that sufficient levels of effort are committed to the project, there is no scientific, budgetary, or commitment overlap, and only the funds necessary to the approved project are included in the grant award.

In addition, NIH applicants and recipients must request and receive approval for the inclusion of any foreign components of an NIH award. A foreign component is the performance of any significant scientific element or segment of the project outside of the United States, either by the recipient or by a researcher employed by a foreign organization, whether or not grant funds are expended.

Among other obligations, the applicant organization must certify, and in some cases submit assurances, that they comply with the public policy requirements provided in the NIH Grants Policy Statement. These requirements are intended to ensure that recipient organizations handle their Federal awards responsibly. While NIH maintains oversight of our awards, we entrust our recipient organizations with the responsibility and accountability for successfully administering their grant award, including prudent fiscal management and other requirements spelled out in the NIH Grants Policy Statement.

NIH will take action and has taken action where appropriate under its authority to address such concerns as part of its proper oversight, compliance, and stewardship roles. As an example, when NIH identifies noncompliance with the terms and conditions of award, it may take actions consistent with the regulatory requirements found in 45 CFR 75.207 and 75.371 for grants and FAR 52.227–11 for contracts. Depending on the severity and duration of the noncompliance, NIH may decide to take one or more actions, which are also described in the NIH Grants Policy Statement, Section 8.5, Specific Award Conditions and Remedies for Noncompliance, including imposing specific award conditions, disallowing costs, withholding future awards for the project or program, suspending the award activities, making a referral for suspension or debarment, or terminating the award.

Protecting the Integrity of the Peer Review System

All participants in the NIH peer review system are responsible for promoting integrity. Maintaining integrity—including obligations of reviewers to keep application information confidential and secure, consistent with their certifications—in the peer review process is essential for ensuring robust exchange of scientific opinions and providing reliable input to NIH about which research projects it should support and maintaining public trust in science.

In recent years, NIH has taken numerous steps to protect the integrity of the peer review process. In addition to issuing several Guide Notices and blogs on the confidentiality and integrity of peer review, NIH has referred many cases to the HHS Office of Inspector General for consideration of further action, including referrals for debarment or suspension, as well as removed the affected individuals from peer review service. Also, in the end of 2018, reviewer conflict of interest certifications were converted to completely electronic format, enabling more thorough assessment of compliance across the agency and in cases of individual breaches.

The NIH Office of Extramural Research (OER) has expanded its internal training for NIH Scientific Review Officers (SROs) to raise their awareness of integrity concerns. OER held three interactive training sessions on peer review integrity in the last year, each event drawing hundreds of SROs. These events covered case studies largely based on actual events and stimulated lively discussion of the best course of action in each scenario. The NIH is also working to implement recommendations from the NIH Advisory Committee to the Director on Foreign Influences on Research Integrity that focus on peer review integrity. Further, NIH continues to explore new technologies and ideas to protect the integrity of the peer review process. For example, a new dashboard is being developed to assist the Office of the Director

in identifying data needed to review possible peer review integrity violations. Finally, policies for permissions to access certain information are being re-assessed. Taken together, these efforts to communicate internally and externally, as well as modernize controls, are raising the profile on peer review integrity concerns and reducing risks.

RESEARCH ON SOCIAL MEDIA IMPACTS

Question. Dr. Collins, as a father of a 14 year old, I understand the role that cell phones, social media, and video games play in an adolescent's life. There is a lot of competing research available that shows the potential mental and emotional effects that media may play. Conversely, media also may be a resource to find social and emotional support for teens. Can you discuss what role NIH is playing in this research? Specifically, can you provide a few examples of what type of studies you are doing?

Answer. NIH is vigorously pursuing this area of research. Several NIH Institutes and Centers, including the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), are researching the effects of increasing use of media by children and adolescents. New evidence shows that screen time use is growing with unknown long-term effects on health and development. Early data from the NIH-funded Adolescent Brain Cognitive Development (ABCD) study shows that only 37 percent of children in the study met the less than two hours per day of recreational screen time recommended by American Academy of Pediatrics (AAP) guidelines. According to the AAP, 95 percent of teens have access to a smartphone, and 45 percent say they are online "almost constantly." In April 2019, the World Health Organization issued new guidelines stating that to grow up healthy, "children under five must spend less time sitting watching screens," emphasizing that screen time should be replaced with interactive non-screen-based activities.

NIH is committed to learning more about this issue. Just last year, NICHD hosted a workshop on media exposure and early child development, bringing together experts in this new field to share their individual perspectives regarding research gaps. Recommendations from some of the workshop panelists included developing meaningful measures of the impact of exposures to media, conducting neuroimaging research to look at the effects on developing brains, and parent education approaches. A recent NICHD-funded study found that exposure to media violence is a strong predictor of aggression and that parental monitoring is a significant factor against aggressive behavior. At the same time, social media can have positive effects; through its Adolescent Trials Network, NICHD is exploring the use of an interactive smartphone app as an intervention to help prevent the spread of HIV. Another study funded in 2018 is exploring whether books presented on a screen or with interactive enhancements confer the same benefits to a child's reading skills and socio-emotional development as print books. Screens also have been associated with delayed or insufficient sleep, which can lead to a number of chronic medical conditions in children and adolescents; another NICHD-funded study is exploring whether the light emitted by screens and other mechanisms affect children's circadian clocks.

The ABCD[9] is a longitudinal study of close to 12,000 children beginning at age 9–10 and continuing through adolescence and into early adulthood to understand how the experiences of adolescence shape brain, cognitive, social, and emotional development. When the children are 9 and 10, they are asked questions about how much time they spend on different activities related to digital media (e.g., watching TV, playing video games, on social media, texting, video chatting). As they get older, they will be asked more in-depth questions about technology use. These data can then be correlated with other assessments within the study such as structural and functional MRI and measures related to mental health, cognition, and sleep, as well as be tracked over time as they mature. This comprehensive data set, led by the National Institute on Drug Abuse and supported by NICHD, the National Institute on Alcohol Abuse and Alcoholism, and the National Cancer Institute (NCI), will be disaggregated by sex, racial/ethnic group, and socioeconomic status, to allow researchers to address numerous questions related to adolescent brain development, thus informing future prevention and treatment efforts and public health strategies.

[9] https://abcdstudy.org/.

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

PULMONARY FIBROSIS

Question. I have a question for you about pulmonary fibrosis, a devastating disease that affects many people in my State. A major area of interest in pulmonary fibrosis-related research is patient-centered clinical research—research that directly addresses issues of most importance to those suffering from the disease. This would include studies looking at reducing hospitalizations, improving symptoms, and prolonging life. For example, researchers are currently examining the chronic cough that pulmonary fibrosis patients cite as one of the symptoms that most affects their quality of life.

In the context of pulmonary fibrosis, what are the NIH and the NHLBI doing to support clinical researchers focused on patient-centered outcomes, and how they are promoting the use of novel data sources such as real-world registries, wearables and other technology?

Answer. The NHLBI continues to support a wide array of clinical trials and fundamental research studies as part of a multi-pronged approach to identify and enhance treatments for patients who suffer from pulmonary fibrosis (PF).

In the fundamental discovery science area, NHLBI-funded researchers are studying the mechanisms of lung fibrosis. One research team recently found that fibrotic cell invasion in PF could be driven by a problem with immune checkpoints, which are cell surface proteins that keep immune responses in check. These same proteins are hijacked by cancer cells to evade the immune system, and are the target for a new class of cancer drugs, suggesting that similar drugs could be used to treat PF.[10] Another group's research suggests that toxic byproducts of oxygen consumption (reactive oxygen species) may contribute to lung injury in idiopathic PF (IPF), which has led to a clinical trial of a potential new drug.[11]

NHLBI supports trials evaluating a number of other potential therapies that target different aspects of pathology in IPF. Two multi-site clinical studies are investigating a combination of therapies that target autoantibodies—which stimulate the immune system to attack the body's own tissues; in PF, certain autoantibodies are known to cause acute breathing exacerbations.[12] NHLBI's Pulmonary Trials Cooperative supports an ongoing study of antimicrobial therapy to reduce the risk of hospitalization and death from PF.[13] Additionally, NHLBI's Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases (CADET) program conducts preclinical research to help translate new understanding of disease mechanisms into better treatment for lung diseases, and is a developing potential new therapeutics for PF.

The NHLBI also strongly encourages investigators to utilize patient registries, such as the Pulmonary Fibrosis Foundation's registry, whenever appropriate to identify, recruit, and retain patients for clinical research, including intervention trials and studies to better understand the disease process. Several current funding opportunities allow PF researchers to leverage existing registries and resources.

The NHLBI also encourages PF researchers to contribute and use whole genome sequencing data that is available through our Trans-omics for Precision Medicine (TOPMed) program. TOPMed is one of three massive datasets that researchers will be able to access and query during a pilot phase of the NIH Data Commons, a cloud-computing environment that is part of the NIH Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) initiative. The NHLBI is also developing another resource called Data Storage, Toolspace, Access and analytics for biG-data Empowerment (DataSTAGE) that will integrate TOPMed and other datasets with analytical tools to provide computing power that will help researchers explore precision medicine for PF and other disorders.

The NHLBI and other Institutes continue to support the development of technologies to ameliorate symptoms such as cough in patients with chronic lung diseases, including PF, in part through our small business research programs. For example, researchers supported by the National Institute on Aging (NIA) are developing a wearable monitoring device to better assess patients with chronic respiratory disease.[14]

The NHLBI also recognizes that aging has a significant impact on disease progression in patients with fibrotic lung diseases, and that there is a need for im-

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[10] https://www.ncbi.nlm.nih.gov/pubmed/30763282.
[11] https://clinicaltrials.gov/ct2/show/NCT03865927.
[12] https://clinicaltrials.gov/ct2/show/NCT03286556
and https://clinicaltrials.gov/ct2/show/NCT01969409.
[13] https://clinicaltrials.gov/ct2/show/NCT02759120.
[14] https://projectreporter.nih.gov/project__info__details.cfm?aid=9465334.

proved methods and tools to account for the interplay between aging and fibrosis. To this end, the NHLBI developed an initiative aimed at Deciphering the Molecular Landscape of Lung Aging in Humans,[15] which is supporting four projects, including a Normal Aging Lung Atlas that will catalog dynamic gene expression changes in aging lung tissue at the single-cell level.[16]

VASCULAR DEMENTIA

Question. Vascular dementia is the second most common form of dementia, after Alzheimer's disease, affecting almost a third of people over age 70. The NIH just completed the first randomized clinical trial demonstrating that lowering of systolic blood pressure significantly reduces the occurrence of mild cognitive impairment, which is an established risk factor and often a precursor for dementia.

As the incidence of dementia continues to rise, what is NHLBI doing to understand the connection between heart health and brain health—e.g. vascular dementia? What can people do to prevent it?

Answer. Cardiovascular disease (CVD) is increasingly recognized as an important contributor to cognitive impairment and dementia. Fortunately, the science also suggests that maintaining a healthy heart can help maintain a healthy brain. A recent Alzheimer's Disease-Related Dementias (ADRD) Summit at NIH included a discussion of vascular dementia and how to continue to move the field forward.[17]

NIH is already leveraging several of its long-established cohort studies to better understand the connections between heart disease and dementia. NHLBI's Framingham Heart Study began 70 years ago, and has since expanded to include three generations of participants. The study has found that many of the risk factors for dementia are the same as those for heart disease, such as high blood pressure, cigarette smoking, lack of physical activity, obesity, and diabetes. A recent NIH-supported analysis of Framingham data found that high blood pressure during mid-life increases the risk of dementia later, suggesting that there are potential cognitive benefits from managing blood pressure in mid-life.[18]

Several NIH cohort studies focused on minority populations have added new objectives to better understand the connection between vascular risk factors and brain health. NHLBI's Jackson Heart Study of CVD in African Americans was renewed in August 2018, and new clinical exams beginning in 2020 will include tests of cognitive function as well as brain imaging. Additionally, the National Institute of Neurological Disorders and Stroke (NINDS) is supporting projects that leverage data from cohort studies such as the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS). To better understand and prevent risk of vascular brain disease in women, participants from the NHLBI-supported Women's Health Initiative are part of the Women's Health Initiative Strong & Healthy (WHISH), trial which is testing whether increasing physical activity will reduce the risk of CVD and cognitive decline in older women.[19]

In the basic research arena, the Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease (M²OVE-AD) Consortium, developed by the NIA in collaboration with NINDS, brings together six multi-disciplinary research teams to use a variety of computational and animal model approaches to better understand the complex molecular mechanisms by which vascular and metabolic risk factors influence the development of Alzheimer's and related dementias, with the ultimate goal to identify therapeutic targets and biomarkers.[20]

It is now known that brain changes typically begin years—if not decades—before people show symptoms, which suggests that a window of opportunity exists to prevent, slow, or delay the onset of cognitive decline. A recent analysis of the Framingham Heart Study examined whether adherence to the American Heart Association's (AHA) Cardiovascular Health Guidelines was associated with improved brain health. The analysis found a lower risk of incident stroke, dementia, cognitive decline, and brain atrophy among participants who adhered to the AHA recommendations, which includes maintaining a healthy body mass index, healthy diet, nonsmoking status, normal total cholesterol, normal blood pressure, and physical activity.[21]

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[15] https://grants.nih.gov/grants/guide/rfa-files/rfa-hl-19-012.html.
[16] https://projectreporter.nih.gov/project_info_description.cfm?aid=9657483.
[17] https://meetings.ninds.nih.gov/?ID=21149.
[18] https://www.ncbi.nlm.nih.gov/pubmed/29117954.
[19] https://whish.stanford.edu/about/.
[20] https://www.nih.gov/news-events/news-releases/decoding-molecular-ties-between-vascular-disease-alzheimers.
[21] https://www.ahajournals.org/doi/full/10.1161/strokeaha.115.012608.

A 2017 National Academies of Sciences report supported by NIH concluded that there is encouraging but inconclusive evidence for several potential approaches to guard against cognitive decline and dementia, including blood pressure management for people with hypertension, increased physical activity, and cognitive training.[22] Recent NIH-funded studies add to the weight of evidence that aggressive treatment of hypertension may protect against cognitive decline. The NIH-funded Systolic Blood Pressure Intervention Trial (SPRINT) trial investigated whether aggressive systolic blood pressure reduction—down to less than 120 mm Hg, rather the prior target of 140 mm Hg—could reduce the risk of heart attack, stroke, and death in people over age 50 who have hypertension. A sub-study, the SPRINT Memory and Cognition IN Decreased Hypertension (MIND) trial, evaluated whether this aggressive treatment would also lower the risk of dementia. These studies were stopped early because the treatment clearly protected against CVD. After about 5 years of follow-up in SPRINT MIND, there was no significant change in dementia risk, perhaps because of the study's shortened duration. However, there was almost 20 percent lower risk of mild cognitive impairment, a well-established precursor of dementia.[23]

QUESTIONS SUBMITTED BY SENATOR CINDY HYDE-SMITH

OPIOID ADDICTION

Question. Dr. Collins, how is NIH investing in research to identify genetic components that may make particular individuals more susceptible to opioid addiction? What is the current status of the science in this area? Are additional funds needed to expand this research?

Answer. Many individuals affected by OUD have a family history of addiction to opioids or other substances, however, research to date indicates that OUD does not have a clear pattern of inheritance. The increased risk among members of an affected family is likely due in part to shared genetic factors, but it is also likely related to environment and other non-genetic influences that are shared by family members.

Separating the complexities of genetic and non-genetic factors that affect OUD risk is a crucial pillar of efforts to stem the tide of the opioid crisis and advances NIH's broader goals of understanding the mechanisms underlying addiction to inform effective prevention and treatment strategies. Accordingly, NIH has fostered a robust and multidisciplinary research portfolio to examine the genetic underpinnings of OUD. There are currently 67 active NIH-funded projects focused on opioid addiction and genetics, as identified in NIH's public database, RePORTER. Some of these projects are highlighted below.

One of the common tools in NIH's arsenal to investigate the role of genetics in disease is a genome-wide association study, or GWAS. A GWAS involves examining genetic variations (genotypes) across the complete sequences of DNA, or genomes, of many different people to find genetic variants associated with a disease or trait (phenotypes). There have been six GWAS projects studying OUD phenotypes that identify several single nucleotide polymorphisms (SNPs), or variations in a single DNA nucleotide, as potentially significant. These variations are being examined to validate their association with OUD. The National Institute on Drug Abuse's Genetics Consortium, founded in 1999 to coordinate efforts of investigators studying substance use disorders and addictive behaviors, is currently conducting its own GWAS, which includes samples from more than 10,000 people. Recent work in psychiatry genetics suggest that sample sizes larger than 10,000 are needed to identify genome wide significant results.

In addition, NIDA is seeking to leverage resources of commercial companies to identify genetic variants for prescription opioid misuse and has issued a Request for Information via FedBizOpps to identify companies that can execute such an initiative (Solicitation 75N95019R00053: Addressing the Opioid Crisis: Genetic Variants for Prescription Opioid Abuse).

Current Status of the Science: While research in this field is still underway, there is already a body of evidence that suggests a few key themes in the complex interplay between genetics and addiction:

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[22] http://www.nationalacademies.org/hmd/Reports/2017/preventing-cognitive-decline-and-dementia-a-way-forward.aspx.

[23] https://jamanetwork.com/journals/jama/fullarticle/2723256.

—The dose of methadone needed to successfully treat OUD is affected by genetic variations in the mu opioid receptor gene and in the gene for the enzyme that metabolizes methadone.[24,25,26]
—Genetic variations in the mu opioid receptor gene are also associated with risk for heroin addiction and with severity of heroin addiction.[27,28,29,30]
—Copy Number Variations (CNVs) (or variability in the number of times a sequence of DNA is repeated) are associated with opioid dependence. In one sequence, a chromosomal deletion is associated with being protective against opioid dependence, and duplication of the same part of the chromosome increased risk for opioid dependence.[31]
—Variations in genes that code for proteins associated with the signaling of glutamate, a widespread neurotransmitter in the brain, have also been associated with development of opioid addiction and regulation of opioid withdrawal.[32,33,34]
—A gene coding for a protein that is important for the way neurons form connections with one another regulates opioid tolerance and opioid-induced hyperalgesia.[35]

Question. Are additional funds needed to expand this research?

Answer. Investing in research is fundamental, and NIH will continue to explore opportunities to expand the scope and impact of genetic research on OUD. For example, an expert panel convened by the NIDA Genetics Consortium recently highlighted the value in conducting a GWAS on opioid naïve surgical patients to identify genetic variants associated with persistent opioid use and other opioid-related outcomes. This would be an opportunity to potentially identify genetic variants among surgical patients who become opioid dependent.

QUESTIONS SUBMITTED BY SENATOR JAMES LANKFORD

FETAL TISSUE/STEM CELLS

Question. During an appropriation hearing in the House of Representatives, Rep. Andy Harris asked you about the ongoing fetal tissue research at NIH, but there were some outstanding questions from his line of questioning. I share Rep. Harris' concern over the use of fetal tissue research at NIH and would like more information as it relates to ongoing studies that use fetal tissue research.

From my understanding, you recently extended a fetal tissue contract with the University of California San Francisco (UCSF).

From where is the tissue obtained that UCSF is providing to NIH?

Answer. UCSF obtained fetal tissue as it became available from elective and legal abortions performed at the UCSF clinic in San Francisco and that would otherwise be discarded. Per the June 5, 2019, statement from the Department of Health and

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[24] Smith AH, Jensen KP, Li J, et al. Genome-wide association study of therapeutic opioid dosing identifies a novel locus upstream of OPRM1. Mol Psychiatry 2017;22:346–52.

[25] Crist RC, Doyle GA, Nelson EC, et al. A polymorphism in the OPRM1 3'-untranslated region is associated with methadone efficacy in treating opioid dependence. The pharmacogenomics journal 2018;18:173–9.

[26] Dennis BB, Bawor M, Thabane L, Sohani Z, Samaan Z. Impact of ABCB1 and CYP2B6 genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction: a systematic review and meta-analysis. PloS one 2014;9:e86114-e.

[27] Schwantes-An TH, Zhang J, Chen LS, et al. Association of the OPRM1 Variant rs1799971 (A118G) with Non-Specific Liability to Substance Dependence in a Collaborative de novo Meta-Analysis of European-Ancestry Cohorts. Behavior genetics 2016;46:151–69.

[28] Hancock DB, Levy JL, Gaddis NC, et al. Cis-Expression Quantitative Trait Loci Mapping Reveals Replicable Associations with Heroin Addiction in OPRM1. Biological Psychiatry 2015.

[29] Zhang Y, Picetti R, Butelman ER, Ho A, Blendy JA, Kreek MJ. Mouse model of the OPRM1 (A118G) polymorphism: differential heroin self-administration behavior compared with wild-type mice. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2015;40:1091–100.

[30] Xu J, Lu Z, Xu M, et al. A heroin addiction severity-associated intronic single nucleotide polymorphism modulates alternative pre-mRNA splicing of the ? opioid receptor gene OPRM1 via hnRNPH interactions. J Neurosci 2014;34:11048–66.

[31] Li D, Zhao H, Kranzler HR, et al. Genome-wide association study of copy number variations (CNVs) with opioid dependence. Neuropsychopharmacology 2015;40:1016–26.

[32] Nelson EC, Agrawal A, Heath AC, et al. Evidence of CNIH3 involvement in opioid dependence. Mol Psychiatry 2016;21:608–14.

[33] Reti IM, Crombag HS, Takamiya K, et al. Narp regulates long-term aversive effects of morphine withdrawal. Behavioral neuroscience 2008;122:760–8.

[34] Crombag HS, Dickson M, Dinenna M, et al. Narp deletion blocks extinction of morphine place preference conditioning. Neuropsychopharmacology 2009;34:857–66.

[35] Donaldson R, Sun Y, Liang D–Y, et al. The multiple PDZ domain protein Mpdz/MUPP1 regulates opioid tolerance and opioid-induced hyperalgesia. BMC Genomics 2016;17:313.

Human Services, the contract expired on June 5, 2019, and there will be no further extensions.[36]

Question. How old are the fetuses that were obtained from UCSF that are used in the study?

Answer. The contract required the delivery of humanized mouse models. The contractor proposed the collection of human fetal tissue in order to create the humanized mouse models. NIH did not specify gestational age of the tissue being collected. As noted above, this contract expired on June 5, 2019, and there will be no further extensions.

Question. Why was the decision made to extend this contract before HHS finished its audit of fetal tissue research?

Answer. The contract with UCSF had an option year that needed to be exercised prior to the completion of the HHS audit. The contract was extended to ensure continuity of service until the audit is completed and a final decision was made about the contract. As noted above, this contract expired on June 5, 2019, and there will be no further extensions.

Question. How many studies is NIH conducting with fetal tissue?

Answer. The Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) provides official NIH figures on research spending by category. For fiscal year 2018, RCDC lists 200 grants and projects that involve research with human fetal tissue.[37] Please also see the June 5, 2019, statement from the Department of Health and Human Services about NIH-supported research using human fetal tissue.

Question. The research conducted by the NIH affords invaluable knowledge and understanding of the infectious diseases we face today. Indisputably, NIH funding is vital to improving healthcare and protecting American lives. That being said, we must ensure that we hold taxpayers' dollars with highest regard and direct our limited resources to projects that not only better our country but reflect the will of the people.

As revealed by the Select Panel on Infant Lives investigation, Planned Parenthood officials have admittedly changed abortion procedures to procure intact fetal body parts for sale. The fact that an industry has been created around the sale of aborted baby parts is deeply disturbing, and I firmly believe we must do all that we can to ensure taxpayers' dollars are used responsibly and ethically when it comes to federally funded research involving fetal tissue.

What steps has NIH taken to partner with hospitals to procure fetal tissue that has been donated after a spontaneous abortion or miscarriage as opposed to tissue that is acquired after an elective abortion?

Answer. NIH funded a major effort through five tissue bank programs to collect and examine tissue donated from women who had spontaneous abortions or ectopic pregnancies. The results were published in the Journal of the American Medical Association in 1995.[38] From over 22,000 obstetric admissions, tissue from 1,250 spontaneous abortions and 247 ectopic pregnancies was obtained. Most of the specimens recovered consisted of maternal or extraembryonic tissue. Of the embryonic collections, less than 1 percent would have been useful for clinical use. 71 percent of embryonic samples were degenerated; 79 percent had bacterial contamination (despite use of aseptic collection techniques); and 40 percent had chromosomal abnormalities.

Question. Has NIH considered limiting its procurement of fetal tissue obtained this way? If not, please explain why.

Answer. NIH-funded research summarized above has established that fetal tissues from miscarriages (spontaneous abortions) and ectopic pregnancies are not feasible sources for research. Please also see the June 5, 2019, statement from the Department of Health and Human Services about NIH-supported research using human fetal tissue.[39]

Question. Since President Obama's Executive Order 13505 "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells" in March 2009, NIH has had wide access to human embryonic stem cells. As you know, this EO revoked a previous EO from President Bush that outlined ethical principles for stem cell research.

As you know, some may claim that because stem cells themselves are not human embryos, there is no need to limit the amount available. But because the cells come

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[36] https://www.hhs.gov/about/news/2019/06/05/statement-from-the-department-of-health-and-human-services.html.

[37] https://report.nih.gov/categorical__spending.aspx.

[38] https://jamanetwork.com/journals/jama/fullarticle/385456.

[39] https://www.hhs.gov/about/news/2019/06/05/statement-from-the-department-of-health-and-human-services.html.

from human embryos, NIH has an ethical obligation to value and honor the human life that contributed to such cells.

While I have received some information on the types of research in which NIH uses "human embryonic stem cells (hESCs)", I am unaware of any validated, successful patient treatment from embryonic stem cells.

Additionally, as you know alternatives to embryonic stem cell research exist. In 2012, the Nobel Prize in Physiology or Medicine was awarded to two researchers for their discovery of induced pluripotent stem (iPS) cells, which mimic the qualities of embryonic stem cells but do not use embryos in any way. Similarly, NIH has had great success in treating and curing more than 70 diseases using adult stems cells and iPS cells. Despite this, it is my understanding that NIH continues to expand its embryonic stem cell research to cell lines not already included on the NIH Human Embryonic Stem Cell Registry.

How many new cell lines has NIH added to its Registry since EO 13505 was enacted?

Answer. Executive Order 13505 directed NIH to issue new guidance on research with human stem cells, including human embryonic stem cells (hESCs).[40] NIH subsequently issued the NIH Guidelines for Human Stem Cell Research (Guidelines) on July 7, 2009.[41] The Guidelines established strict new criteria for the NIH Director to determine the eligibility of the use of specific hESC lines in NIH-funded research. The NIH Director has approved 398 hESC lines for use in NIH-supported research under this policy, including 10 of the 21 cell lines that were also eligible for use under the policy of the prior administration. The NIH Director has also determined that 70 hESC lines are not eligible for use in NIH-supported research, primarily due to inadequacies in the embryo donation consent process.

Question. Why has NIH chosen to add more cell lines to its registry instead of using cells already on the registry?

Answer. Part of the stated purpose of the Executive Order was " . . . to expand NIH support for the exploration of human stem cell research." So, NIH developed a new policy, which included stricter new requirements regarding the embryo donation process. Under current policy, hESCs can only be used by NIH funded researchers if the embryos were created using IVF for reproductive purposes, no longer needed by the parents, and the embryos were donated by those parents with voluntary, written, informed consent. NIH also included new requirements that certain information be given to the potential donors during the consent process, such as what will happen to the embryos, and how long they have to change their minds.

Some of the newer hESC lines have characteristics that are more suitable for clinical use, including reduced exposure to animal products and viruses. Some are also more flexible in their ability to form different tissue types. There are more than 100 hESC lines approved under the current policy that have mutations associated with particular diseases, providing useful cell models for studying those diseases.

Question. Why has NIH not used IPS cells for research instead of using hESCs?

Answer. NIH funds a range of stem cell research, using induced pluripotent stem cells (iPSCs) as well as hESCs. In fiscal year 2018, NIH awarded $468 million for human iPSC research and $278 million for hESC research. NIH is currently funding a significant amount of pre-clinical research using iPSCs. For example, an investigator in the National Eye Institute's intramural program is developing an iPSC-derived cell therapy for age-related macular degeneration.[42] There are also other investigational cell therapies developed from human induced pluripotent stem cells (hiPSCs) in clinical trials now (not funded by NIH) for age-related macular degeneration, graft versus host disease, and Parkinson's disease.

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

CHIEF DATA STRATEGIST

Question. For the past 3 years, this committee has urged NIH to focus on developments in data science as it relates to biomedical research. What is possible to achieve by harnessing the vast amount of data produced in science is still unknown. But what we do know, is with proper leadership, vision, and tools, big data has the potential to help scientists unlock infinite breakthroughs and discoveries in biomedical research. At the direction of this committee, in May 2018 NIH released a strategic plan for data science, which includes recommendations to advance data in-

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[40] https://www.govinfo.gov/content/pkg/FR-2009-03-11/pdf/E9-5441.pdf.
[41] https://stemcells.nih.gov/policy/2009-guidelines.htm.
[42] https://irp.nih.gov/pi/kapil-bharti.

frastructure and data stewardship in support of the data ecosystem at NIH and improve NIH's expertise in this space.

After a year of efforts to recruit for the new CDS position, NIH still has not filled this role.

What is the status of the job search for the Chief Data Strategist? Please include details on the recruitment, number of applicants and interviews, significant next steps, and timeline for completion. Are there specific obstacles to filling this role that NIH needs to address?

Answer. The recruitment for the NIH Chief Data Strategist is currently open for receiving applications, until filled. The recruitment for this position opened on May 9, 2018. To date, NIH has received 59 application packages which met the basic qualifications for the position, held rating meetings, and conducted interviews. An external search firm was secured to work in concert with the search committee to seek and encourage highly qualified candidates to apply. Over 20 ads were placed online with periodicals, data science organizations, and diversity associations. Currently, a video is being produced to highlight the data science activities at NIH, which will be released to encourage candidates to apply to this position. The recruitment timeline is currently open ended.

Data science is a burgeoning field of study, involving both private sector and academic leaders. The NIH is hoping to fill this position with an individual who has the knowledge and unique skill set needed to accelerate NIH progress in data science and to expand collaborations worldwide. As you note, it has been exceedingly challenging to attract someone that would bring the unique combination of knowledge and skills to the position. Federal salary limits are one limiting factor and the constraints related to financial holdings that result from Federal employment are another. The NIH is committed to filling this position as soon as possible and is determined to fill the position with the ideal candidate.

Question. Since the recruitment process is taking a considerable amount of time, what is NIH doing during this interim period, prior to hiring a CDS, to move the work forward?

Answer. Executive leadership of data science efforts at the NIH continues to be provided by the Interim Associate Director for Data Science, a position temporarily being filled by the Principal Deputy Director, NIH. The Scientific Data Council, co-chaired by the Director, National Institute of General Medical Sciences, and the Director, National Institute of Biomedical Imaging and Bioengineering, is also providing advice and oversight to ensure forward movement on trans-NIH data science activities. Other executive staff, including the Directors of the Center for Information Technology and the National Library of Medicine have been playing key roles in moving forward critical data science efforts. The Director of the NIGMS Division of Biomedical Technology, Bioinformatics, and Computational Biosciences is providing essential leadership for, and helping to fully operationalize, the Office of Data Science Strategy (ODSS). Other Office of the Director staff are also playing key roles for activities that are being led and funded by ODSS. While we have not yet been able to fill the Chief Data Strategist position, we have made significant progress in implementing components of the NIH Strategic Plan for Data Science.

Question. Given the challenges of bringing someone with the appropriate skills, vision and background into the CDS position, what alternatives is NIH exploring?

Answer. As noted above, NIH contracted with an external search firm to work closely with the search committee to seek and encourage highly qualified candidates to apply. Over 20 ads were placed online with periodicals, data science organizations, and diversity associations. A video is being produced to highlight the data science activities at NIH which will be released to encourage candidates to apply to this position. In the meantime, NIH leadership is considering whether other NIH employees could fill this vacancy on a temporary basis.

Question. Has NIH consulted with organizations that face similar challenges, such as DoD, NASA, and universities attempting to solve some of the same cutting edge data challenges?

Answer. Yes. Through both formal interagency processes and informal leadership and staff level conversations, NIH consults and shares information with other Federal research agencies facing similar challenges. As part of the search for the CDS, we have also engaged in extensive outreach, including to other Federal agencies, e.g., Department of Energy and the National Science Foundation.

We are continuing efforts to find the best candidate for this critical position at NIH. Some important new approaches we will be taking are listed below:

—NIH is about to launch a social media and marketing campaign for the CDS position—possibly as early as the week of May 28. You may see Twitter and Facebook posts from NIH, Dr. Collins, the CDS Search Committee co-chairs, and various other NIH-related handles. NIH is also asking other Federal gov-

ernment agencies to help amplify our posts. An executive search firm will be helping NIH cross-promote on LinkedIn.
—NIH has produced a final cut of a 5-minute video about the position. View on YouTube here: https://youtu.be/92arhggy4xI.
—Dr. Collins will use his blog to highlight the important of this position to NIH's future with an embedded version of the video.
—An easier-to-use URL for the position is now available: www.nih.gov/CDS http://www.nih.gov/CDS.
—NIH will make additional efforts to identify and capitalize on NIH leadership that have personal connections with Silicon Valley and other tech company executives/VIPs who may have good candidates to recommend.
—A slide will be provided for use by NIH leadership in any presentations they are making to the tech community.
—A 30 second teaser video, based on the YouTube video linked above, will be released as part of a social media marketing campaign to attract candidates.

Question. Last year, the Committee assumed that implementation of certain components of the strategic plan—including developing performance measures and specific milestones for the plan's objectives—was delayed due to the open job search. What, if any, steps in the strategic plan have been implemented to date?

Answer. The NIH has moved forward in implementing multiple components of the NIH Strategic Plan for Data Science. Currently, a team of NIH employees detailed to the ODSS is coordinating the efforts of nearly thirty implementation working groups with members representing nearly all NIH Institutes and Centers. ODSS has also established a Technical Implementation Working Group composed of high-level data science experts across NIH to advise the Office on technical matters related to implementation tactics. A non-exhaustive summary of current activities aligned with each goal of the strategic plan is provided below:

Goal 1: Support a highly efficient and effective biomedical research data infrastructure.
—ODSS executed a contract with BioTeam, Inc. to develop a basic needs requirement document that would directly inform the infrastructure development of a NIH-wide data ecosystem that meets FAIR principles. The contractor is currently in the process of collecting data ecosystem use cases and conducting a gap analysis across high-profile NIH data systems. A final report is anticipated in September 2019.
—ODSS is providing technical assistance to the NIH Office of Science Policy (OSP) in the review of current policies regarding Data Access Committees to streamline and increase the efficiency of review.
—The National Center for Biotechnology Information and CIT have developed an initial strategy for a trans-NIH approach to user authentication and authorization for access to data sets. This technical solution will be developed into a testable prototype in the next few months.
—The STRIDES Initiative, a NIH partnership with industry-leading cloud service providers (currently, Google and Amazon) to provide discounted cloud storage and compute access to biomedical researchers, continues to migrate high-value data sets to cloud platforms. ODSS is providing oversight of this CIT-managed initiative and has engaged nearly 40 data programs in both the intra- and extra-mural communities. NIH is developing the policies and procedures for making this innovative partnership available to all NIH-funded biomedical researchers in order to accelerate scientific discoveries leading to new health technologies.

Goal 2: Promote modernization of the data-resources ecosystem.
—A strategic plan implementation team co-led by NLM and NIGMS developed new funding opportunity announcements (FOAs) that will address the objective of separating support for databases and knowledgebases and sets forth appropriate resource criteria and review criteria that must be met in order to receive NIH support. These FOAs are currently under review with an anticipated release date this summer.
—This April, NIH held a workshop to share criteria for trustworthiness of data repositories and to educate biomedical data managers on the CoreTrustSeal certification requirements. Information from the workshop will be used to promote sustainable and trustworthy data infrastructures in the biomedical arena. In a related effort, NLM conducted a comprehensive analysis of criteria for open-access data sharing repositories that receive NIHsupport and will soon publish a public request for information to solicit additional input on draft criteria.
—The NIH Scientific Data Council is reviewing how NIH could potentially integrate existing clinical data elements with the industry-adopted fast healthcare

interoperability resources (FHIR) specification to enable the exchange of healthcare, clinical and basic research data across different systems.

Goal 3: Support the development and dissemination of advanced data management, analytics, and visualization tools.

—ODSS is engaged in planning a workshop to bring systems integration specialists from the private sector so that NIH data scientists can learn the latest approaches to the optimization of data analysis tools and algorithms.

—NSF and NIH/ODSS will hold a workshop in June to discuss opportunities for joint funding of data science research programs, with a particular emphasis on AI/ML approaches to solving complex data analysis problems in biology and medicine.

—ODSS executed a contract with FigShare, providing NIH-funded researchers with access to online open access repository where researchers can preserve and share their research outputs, including figures, datasets, images, and videos.

Goal 4: Enhance workforce development for biomedical data science.

—Please refer to NIH's description of efforts in data science workforce development addressed in the response to a specific question for the record on this topic.

Goal 5: Enact appropriate policies to promote stewardship and sustainability.

—The NIH OSP recently completed its analysis of public comments on proposed provisions for a draft data management and sharing policy. OSP is in the process of incorporating the public feedback and will release a draft policy statement for further public consultation.

Question. The Committee included $30 million to support the Chief Data Strategist's work in fiscal year 2019. What is the status of NIH's plan for this funding?

Answer. The NIH has engaged in a multi-step planning process to identify the most pressing trans-NIH needs for the data science funding provided by Congress. The $30 million is being used to advance the trans-NIH data ecosystem—that is, we are working to make currently siloed data storage and workspaces connect (interoperable) by establishing standards, building infrastructure and tools to allow different data repositories to talk to each other, and defining common data elements and standards.

DPCPSI/OFFICE OF STRATEGIC COORDINATION

Question. The Data Commons Pilot Phase was initiated under the New Models of Data Stewardship program, implemented in support of the Strategic Plan for Data Science. This project was supposed to run through fiscal year 2020 and was tasked with developing a four-year roadmap for the data commons. What is the status of this roadmap, how is NIH implementing the associated recommendations, and what are the next steps for this initiative?

Answer. The NIH Data Commons Pilot, part of the Common Fund's New Models of Data Stewardship program, aimed to accelerate new biomedical discoveries by developing and testing a cloud-based platform where investigators could store, share, access, and interact with digital objects (data, software, etc.) generated from biomedical and behavioral research. By connecting the digital objects and making them accessible, the Data Commons was intended to foster novel scientific research that wasn't possible before, including hypothesis generation, discovery, and validation. The program supported the NIH Strategic Plan for Data Science [43] goal to develop new, cutting-edge methods for storing, sharing, and analyzing NIH supported datasets in the cloud.

From 2017–2018, researchers funded as part of the NIH Data Commons Pilot Phase Consortium (DCPPC) tested the best ways to build and implement the cloud-based platform described above. They iteratively experimented with a series of key capabilities needed for the Commons to operate and meet standards for being FAIR—findable, accessible, interoperable, and reusable. Three different and high-value test case data sets helped in setting policies, processes, and architecture for the Data Commons Pilot Phase.

Development of a roadmap for modernizing the biomedical data science ecosystem requires trans-NIH coordination, most appropriately managed by the NIH Office of Data Science Strategy (ODSS). Therefore, ODSS is developing a broad, trans-NIH data ecosystem strategy informed by the tools and best practices developed by the DCPPC. The Common Fund will continue to test, evaluate, and refine a subset of deliverables from the Data Commons Pilot Phase, working with Common Fund programs to establish a cloud-based data ecosystem for Common Fund datasets.

[43] https://datascience.nih.gov/strategicplan.

DPCPSI/OFFICE OF DATA SCIENCE STRATEGY

Question. Research organizations are exploring the best ways to create research data commons. Private sector communities of companies and extramural research institutions, like Sage Bionetworks, Penn State, and Google's datacommons.org have demonstrated success. Even other Federal agencies have successfully established data commons, such as the National Science Foundation big data innovation hubs, and are further along than NIH. Furthermore, we must ensure NIH is also learning from less successful attempts at driving data infrastructure, such as caBIG, which saw little traction in the community and was widely criticized. As good stewards of taxpayer investments, what is NIH doing to avoid "reinventing the wheel" and how is NIH planning to leverage data commons work already being done extramurally?

Answer. NIH appreciates the opportunity to highlight how we are building upon the advances in academia and industry to create a highly integrated biomedical research data ecosystem. A principle stumbling block across data science is the compartmentalization of data—from biomedical research data, disease specific data, health records and data resulting from clinical trials. These data silos impede discovery of commonalities across diseases and inhibit a cross-disciplinary understanding that will rapidly accelerate innovation in the biomedical research enterprise. Our goal at NIH is to leverage data and information from different studies and across diseases to empower investigators to ask new questions and make new discoveries to improve human health.

To do so, NIH is investing in many data commons efforts, including NHGRI ANVIL, NCI Cancer Research Data Commons, All-of-Us Research Program, NIMH Data Archive, NHLBI Data STAGE and others.[44] We have recently completed a NIH Data Commons Pilot study and we have undertaken a comprehensive analysis of this, and the other commons efforts listed above, to learn from our past and current efforts and to determine successful approaches with existing capabilities.

NIH is also working with leading industry partners, including Google and Amazon, and academic collaborators, to leverage those experience, expertise and technologies as we work to connect high-value NIH data systems. An early example of this is the cross-NIH effort to create an industry-standard system that will allow any NIH researcher a single-entry point to NIH data resources, with the appropriate security-enabled data access.

In addition, the National Center for Advancing Translational Sciences' (NCATS) Biomedical Data Translator program is building an informatics platform that aims to bridge the current symptom?based diagnosis of disease with research?based molecular and cellular characterizations through interrogation of relationships across the full spectrum of data types (e.g., disease names, clinical signs and symptoms, to organ and cell pathology, genomics, and drug effects). The Translator is not a database but rather is focused on identifying data integration and inclusion barriers and exploring inferential or predictive models that would provide new insights into biology, health, and disease. The Translator will find and connect existing data, provide previously unknown insights into diseases and possible treatments, and make inferences and predictions even when data are missing to translate basic data science to clinical and public health practices.

Together these, and other efforts articulated in the NIH's Strategic Plan for Data Science, aim to maximize the value of the data generated through NIH-funded efforts to enable biomedical discovery and innovation. Doing so is critical for keeping the United States at the forefront of biomedical research and ensuring continued advances toward improving the Nation's health.

Question. Beyond the efforts in NIGMS, what is the NIH doing to encourage, support and incorporate computational science training in other scientific fields beyond those like genomics and neuroscience which have already embraced it?

Answer. NIH is committed to training the next generation of researchers across biomedical related disciplines, including computer science. Twelve of the agency's

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[44] *NHGRI AnVIL* is designed to be an interoperable resource for the genomics community to co-locate data, storage and computing with commonly used services for analyzing and sharing data.

NCI Cancer Research Data Commons is a virtual, expandable infrastructure to provide secure access to cancer-specific data to allow researchers to analyze, share and store their work, in a cloud environment.

NIMH Data Archive is a collaborative resource that contains human subjects research data for Autism research

NHLBI Data STAGE is a digital environment that allows for access to NHLBI datasets and innovative data analysis capabilities, in a cloud environment.

All-of-Us Research Program provides a cloud-environment to gather and serve data from one million or more people living in the United States.

Institutes, Centers, and Offices (ICOs) support a funding opportunity, the Mentored Quantitative Research Career Development Award (K25), to attract investigators whose quantitative science and engineering research has thus far not been focused on questions of health and disease. This funding opportunity supports professionals with quantitative (e.g., mathematics, statistics, economics, computer science, imaging science, informatics, physics, chemistry) and engineering backgrounds to integrate their expertise with NIH-relevant research. Another cross-NIH effort, Predoctoral Training in Advanced Data Analytics for Behavioral and Social Sciences Research—Institutional Research Training Program (T32), is funding training opportunities for predoctoral students in data analytics for behavioral and social science research and is supported by a number of ICOs. Other trans-NIH funding opportunities are being planned to broaden the expertise of the extramural biomedical community and will be released in the coming months. Additionally, the National Library of Medicine recruits data scientists to work in their institute through several coordinated postdoctoral training programs, and has a joint program with the National Institute of Dental and Craniofacial Research to recruit computer scientists to postdoctoral studies in the dental field. Other ICOs across NIH recruit computational experts to work in their intramural research programs based on the lab's specific needs.

Training programs for NIH staff and extramural researchers who are putting data into Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability Initiative are currently being offered. These trainings target general use of the cloud platforms as well as generic [mock/dummy] tool and dataset use in cloud environments.

NIH has also initiated several fellowships to expand the expertise of the NIH internal workforce, by bringing computationally-savvy individuals to work in NIH offices. For example, through Coding it Forward's Civic Digital Fellowship and the NIH Office of Intramural Training and Education Graduate Data Science Summer Program, ODSS will bring 23 data scientists to NIH campus this summer to be placed in offices and laboratories throughout the agency. Other programs led by NIH to bring computational experts into the Federal workforce include the Emerging Leaders in Data Science Fellowship, led by NIAID, and the Big Data Scientist Training Enhancement Program, co-led by NCI and the Department of Veterans Affairs.

RARE CANCERS

Question. At least 95 percent of 400 known forms of cancer meet the American Cancer Society criteria of affecting fewer than 6 Americans per 100,000 per year, yet in 2018 nearly 80 percent of cancer patients with no approved targeted therapeutic for their cancer have a rare cancer. Many of these cancer patients are faced with decades-old treatment protocols that include harsh chemotherapies which are frequently ineffective for their cancers. What are NIH, NCI and NCATS doing to develop more therapeutics for these neglected rare cancers?

Almost 1 in 3 new cancer diagnoses is for a rare cancer. However, rare cancers suffer from critical gaps in funding, available data, and basic and translational science. In 2017, over 148 forms of rare cancer received no direct funding from NIH, and that gap in spending is associated with a lack of FDA-approved targeted therapies available for those cancers. Simultaneously, just 34 out of 380 forms of rare cancer received almost 40 percent of NIH funding that was directed to rare cancers. What is being doing to encourage greater support for research into rare cancers?

I understand 95 percent of all cancers are rare forms, and increased use of molecular subtyping can lead to more accurate diagnoses of those precise forms. But that is only if this subtyping is done. I understand molecular diagnostics are seldom used for the majority of patients and data on cancer subtypes is rarely shared among researchers and physicians. What can be done to improve molecular analysis for patients, and to permit patients to anonymously and publicly share their data with researchers and drug developers?

A key to understanding and developing targeted cancer treatments is the ability to research tumor cell lines, yet cells lines for rare cancers are frequently difficult to obtain, especially for smaller companies, due to high costs or licensing restrictions. When they are available, they sometimes do not share the genetic profiles of the cancers they are meant to represent. Why is that? How can we change that to accelerate research to save lives in the near-term?

Treatment for pediatric cancers carries a tremendous burden for survivors throughout their childhood and adult lives, frequently due to the use of caustic chemotherapy agents. There is only one currently available targeted therapy that is specifically approved for a childhood cancer, neuroblastoma. What is being done

to ensure that childhood cancers receive appropriate levels of funding for translational research that turns basic science into new therapies?

Over 550,000 Americans were newly diagnosed with a rare cancer in 2018, but SBIRs, which are a major source of translational funds to bridge the drug development 'valley of death', primarily fund common cancers. In fact, in the 5-year span between 2013 and 2017, 262 forms of cancer, all rare, did not receive any directed funding—that's over 65 percent of all types of rare cancer. What is being done to ensure that SBIR funding is addressing the critical translational gap for these neglected rare cancer patients?

Over half a million Americans were newly diagnosed with a rare cancer in 2018. For over 100 of those cancers, there are no available datasets in the most significant microarray repository in the world, GEO. Unfortunately for those patients whose cancers are not represented, they have an almost 7-fold decreased likelihood of having a targeted therapy. What is being doing to ensure that all forms of cancer have significant dataset presence in publicly available data repositories?

Answer. Rare cancers all qualify as rare diseases, which are diseases or conditions affecting fewer than 200,000 people in the U.S. The National Center for Advancing Translational Sciences (NCATS) has several programs and initiatives focusing on rare diseases, including rare cancers. Specifically, the Office of Rare Diseases Research (ORDR) is dedicated exclusively to accelerating treatments and research to benefit rare disease patients.

Advancing research on rare cancers is an important focus across the NCI portfolio as well. As our understanding of cancer expands, we now know it is not one disease, but hundreds, if not thousands, of cancer types and subtypes—a collection of rare diseases. A quarter of all cancer deaths each year are due to rare cancers. Although new treatments are always being developed, finding new effective treatments for rare cancers is challenging for many reasons. Additionally, this translational and clinical research is only possible due to NCI's sustained investment in basic science that advances understanding and progress for all cancer types, including rare cancers.

Question. What are NIH, NCI and NCATS doing to develop therapeutics for these neglected rare cancers?

Answer. Several NCI-supported research efforts aim to advance and accelerate the development of targeted cancer therapies for rare cancer types and subtypes diagnosed in children and adults. The following narrative describes some of the major NCI initiatives that may benefit rare cancer patients, but it is not an exhaustive list of the Institute's investments in rare cancer research.

The cancer research community continues to recognize that cancer is made up of a collection of hundreds, if not thousands, of subtypes defined by these characteristics. NCI-supported research like The Cancer Genome Atlas[45] and the Pediatric TARGET (Therapeutically Applicable Research to Generate Effective Treatments) Initiative,[46] as well as the Pediatric Cancer Genome Project led by Washington University and St. Jude Children's Research Hospital,[47] have been critical to advancing this field. As a result of these efforts and other relevant research, "cancer" is increasingly recognized as a collection of rare cancer subtypes, each of which will likely require a somewhat different treatment. NCI's ongoing efforts include research to support the development and evaluation of precision approaches to cancer therapy—including targeted chemotherapy and immunotherapy, and combination therapy approaches based on the molecular profile of the cancer.

As part of the Cancer Moonshot, NCI launched the Rare Tumor Patient Engagement Network in fiscal year 2018, leveraging the unique resources of the NCI intramural research program and the NIH Clinical Center to bring together national and international investigators, patients, advocacy groups, and industry to comprehensively study rare tumors and provide exceptional patient care. Under the umbrella of this effort, NCI has also launched the Moonshot Pediatric, Adolescent, and Young Adult Rare Tumors (MyPART) Network, a collaboration of scientists, patients, family members, advocates and healthcare providers to find treatments for rare cancers.[48] The MyPART Network will collect samples like blood, saliva, and biopsy tissue from people with rare tumors to study how rare tumors grow, share data from rare cancer samples with other scientists, build new ways of testing new treatments, and design new clinical trials for rare cancers.[49] Another component of this rare tu-

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[45] https://cancergenome.nih.gov/.
[46] https://ocg.cancer.gov/programs/target.
[47] https://www.stjude.org/research/pediatric-cancer-genome-project.html.
[48] https://ccr.cancer.gov/research/cancer-moonshot.
[49] https://www.cancer.gov/nci/pediatric-adult-rare-tumor/about/what-is-mypart.

mors initiative, the NCI Comprehensive Oncology Network Evaluating Rare CNS Tumors (NCI-CONNECT) within the intramural program aims to advance the understanding of rare adult central nervous system (CNS) cancers by establishing and fostering patient-advocacy-provider partnerships and networks to improve approaches to care and treatment. Although all primary adult CNS tumors can be considered rare, NCI-CONNECT is starting with 12 types, each with less than 2,000 patients diagnosed a year. NCI-CONNECT intends to address these challenges and unmet needs by connecting patients, providers, researchers and community organizations to work in partnership.[50]

The NCI-MATCH Trial[51] is an important research program for rare cancers for which there is not a standard of care or cancers that no longer respond to standard treatment. This nationwide trial, which has enrolled patients in all 50 States, analyzes patients' tumors to determine whether they contain gene abnormalities for which a targeted drug exists and then assigns patients to treatment based on the abnormality. Using this approach, the NCI-MATCH trial holds promise for improved treatment options for both common and rare cancers. The trial originally had "set aside" 25 percent of screening accrual to be for rare cancers, to ensure that more common cancers were not over-represented. Ultimately 62.5 percent of the over 6,000 patients screened for MATCH represented rare cancers. However, even with 6,000 patients screened, some trial arms did not complete accrual due to the low frequency of a particular variant in the population. Thus, patients continue to be enrolled in these trial arms through the Rare Variants Initiative. Launched in May 2017, the Rare Variants Initiative casts a wider net for patients through collaborations with additional commercial and academic partners that will help find patients with uncommon genetic variants and let their doctors know they may be eligible for the MATCH trial.

The mission of the NCI Experimental Therapeutics (NExT) Program[52] is to advance clinical practice and bring improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects. For those institutions collaborating with NCI, NCI may leverage its scientific expertise and various contract and grant resources toward the implementation and development of submitted projects. The NCI will partner with successful applicants to facilitate the milestone-driven progression of new anticancer drugs (small molecules, biologics) and imaging agents towards clinical evaluation and registration.

Additionally, NCATS supports the Tissue Chip for Drug Screening Program, which is an innovative program that enables the development of microphysiologic systems to develop human tissues on bioengineered chips. This program seeks to better understand human disease, model human organs and organ systems, and potentially serve as toxicology and drug screening systems. Many rare disease indications have been included in the tissue chip program, including tuberous sclerosis, which is a rare disease that leads to benign tumor growth in the brain. This program is planning to support development of chips that can be used to inform potential clinical trials on rare diseases and, in conjunction with NCI, rare cancers will be included as part of the research focus.

NCATS also supports the Therapeutics for Rare and Neglected Diseases (TRND) and the Bridging Interventional Development Gaps (BrIDGs) programs. TRND supports pre-clinical development of therapeutic candidates intended to treat rare or neglected disorders with the goal of enabling an Investigational New Drug application (IND). TRND works in collaboration with external partners, such as academia and industry on these projects, and TRND provides scientific expertise and resources to further therapeutic development. Researchers working on rare cancers are eligible for assistance from this program. Similarly, BrIDGs assists researchers in advancing promising therapeutic agents thought late-stage pre-clinical development toward an IND and clinical testing. Currently, these programs are working on several rare cancer-related projects, including work on pancreatic cancer and core binding factor (CBF) leukemia.

Notable NCATS programs led through the ORDR relevant to rare cancers include:

—The Rare Diseases Clinical Research Network (RDCRN)[53] provides cooperative awards to multi-center multi-disciplinary consortia who study three or more related rare diseases at a time. This program has supported research into >250 rare diseases since its inception, including some rare cancer-related diseases and conditions. Applications for new consortia members are currently being considered and awards will be announced around June-July 2019. Some of the ap-

[50] https://ccr.cancer.gov/neuro-oncology-branch/connect.
[51] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.
[52] https://next.cancer.gov/entryToPipeline/default.htm.
[53] https://ncats.nih.gov/rdcrn.

plications being considered include rare cancers and cancer-related conditions that may be funded in collaboration with NCI.

—The Bench-to-bedside (B2B) grant program[54] is run by the NIH Clinical Center (CC), and NCATS ORDR supports four B2B awards each year for rare disease indications. These grants are for intramural/extramural partnerships leveraging the CC and other resources to facilitate translating bench research toward clinical trials. Several rare cancer-related B2B grants have been supported through this program over the past 15 years. Some examples of rare cancer and cancer-related B2B awards include, but are not limited to: T-cell adoptive therapy for viral infection after stem cell transplantation and CAR-modified CD8+ memory stem cells targeting B-cell malignancies, among others.

—The Toolkit for Patient-focused Therapies Development ("Toolkit")[55] and the Rare Diseases Registry program (RaDaR)[56] assist patients and patient groups, who play a large role in therapeutics development and research for rare diseases, including rare cancers. Toolkit and RaDaR provide advice, tools, templates and best practices for initiating and furthering rare disease research programs and registries, respectively. Toolkit and RaDaR are web-based freely accessible resources that anyone can access and use.

—The Scientific Conferences (R13 and U13) Grant program[57] provides small grants to help co-fund scientific conferences and meetings. Priority areas for NCATS include translational sciences and rare diseases, including rare cancers. In the past several years, grants have included conferences on rare cancers and cancer-related indications, including, but not limited to, cholangiocarcinoma, cancer vaccines, RASopathies, and cancer immunotherapy, among others.

Question. What is being doing to encourage greater support for research into rare cancers?

Answer. The NIH and the NCI rely heavily on scientific peer review, in which highly trained outside scientists initially review investigator-initiated research proposals and score them based on factors such as scientific merit, potential impact, likelihood of success, and disease burden. Thereafter, the National Cancer Advisory Board conducts a review of the research proposals. NCI does not establish predetermined targets for a specific disease area or research category, and does not set preestablished funding levels for cancer types or specific areas of cancer research. It is important to note that NCI and NIH do not consider disease burden to be limited to how many people are diagnosed with a disease or condition, but rather uses a broader lens to capture the impact of a health condition as measured by mortality, morbidity, financial cost, and other indicators. Accordingly, NIH's Institutes and Centers support special initiatives based on public health need, including burden of disease. Comprehensive portfolio analysis and programmatic evaluation are also critical to these programmatic decisions and development of special initiatives. Examples span common and rare cancers, such as NCI's RAS Initiative, which focuses on molecular alterations in the RAS family of genes and pathways, responsible for driving the development and progression of several common and rare cancers. Other examples include the Cancer Moonshot, which is supporting research relevant across cancer types and scientific areas, and NCI's proposed Childhood Cancer Data Initiative.

In addition, the Institute strives to balance strategic efforts to address public health needs with its basic scientific research portfolio. Basic research, which represents approximately half of the NCI research portfolio, is vital to achieve progress in the cancer types for which little or no progress has been made. Decades of basic research investments from NCI and NIH have demonstrated the value of basic research as a foundation for clinical advances, even though the basic research may lack a direct initial connection to a specific disease, the serendipitous discoveries of basic research illuminate pathways for future clinical breakthroughs.

Question. Molecular diagnostics are seldom used for the majority of patients and data on cancer subtypes is rarely shared among researchers and physicians. What can be done to improve molecular analysis for patients, and to permit patients to anonymously and publicly share their data with researchers and drug developers?

Answer. Detailed molecular characterization of tumors has demonstrated the heterogeneity of cancer and can identify genetic alterations that may allow for the selection of targeted therapies for patients based on the unique profile of a patient's tumor. This is the basis for the NCI-MATCH trial mentioned above. However, it is

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[54] https://clinicalcenter.nih.gov/ccc/btb/.
[55] https://rarediseases.info.nih.gov/toolkit.
[56] https://registries.ncats.nih.gov/.
[57] https://grants.nih.gov/grants/funding/r13/index.htm.

important to point out that targeted therapies currently only exist for a small number of known genetic alterations.

Although comprehensive genomic profiling is technically feasible, its current application in clinical practice is fragmented and there are barriers to wide-spread profiling. These barriers include cost, lack of standardized genomic profiling panels and tumor collection, insufficient evidence of broad-based clinical utility, and lack of infrastructure to harmonize and share data across the clinical and research community.

The NCI is addressing several of these barriers. Precision medicine clinical trials like NCI-MATCH and others seek to provide the evidence of clinical utility of treating a patient based on a unique characteristic of the patient's tumor regardless of the type of tumor. In addition, other NCI research supported through the Cancer Moonshot's direct patient engagement efforts,[58] including the Rare Tumor Patient Engagement Networks mentioned above, will support molecular characterization of patients' tumors, directly engage patients to participate in clinical trials, and share tumor profiling data with the research community and the individual patient participants through a secure linked network of databases.

The NCI has established the Cancer Research Data Commons as a part of a larger National Cancer Data Ecosystem to support precision medicine. The Data Commons will provide an information platform to support the integration of genetic information about patients and their tumors with data on how the tumors respond to therapy. The Data Commons will also incorporate additional data such as imaging and clinical data from patients to identify approaches to cancer care that will improve patient outcomes. Other NCI efforts include the development of a cancer data aggregator to link various data types across the Data Commons and ultimately allow for analysis of multimodal data sets; and an encrypted unique patient identifier to link patient level data while protecting personally identifiable information. The former is critically important to address patient privacy issues that exist with publicly sharing their data.

Cost is an important issue outside of the scope of the NCI mission. However, NCI notes that in March 2018 CMS took an important step in addressing this barrier by finalizing a National Coverage Determination that covers diagnostic laboratory tests using Next Generation Sequencing for patients with advanced cancer.[59]

Question. A key to understanding and developing targeted cancer treatments is the ability to research tumor cell lines, yet cells lines for rare cancers are frequently difficult to obtain, especially for smaller companies, due to high costs or licensing restrictions. When they are available, they sometimes do not share the genetic profiles of the cancers they are meant to represent. Why is that? How can we change that to accelerate research to save lives in the near-term?

Answer. As a public sponsor of biomedical research, NIH, including the NCI, is committed to supporting national and international efforts that encourage the sharing and dissemination of important research resources. NIH also recognizes the need to support reasonable incentive structures that facilitate commercial development or translation of basic research findings. Restricted availability of unique research resources, upon which further studies depend, can impede the advance of research. Conversely, sharing biomaterials, reagents and data in a timely manner has been an essential element to stimulate rapid research progress on many model organisms for biomedical research. The NIH is interested in continuing to ensure that the research resources developed with NIH funding are made readily available in a timely fashion to the research community for further research, development, and application, which will further the research enterprise and accelerate the development of products and knowledge of benefit to the public.

With regard to rare cancers specifically, low incidence rates of rare cancers mean both patients and researchers face unique challenges. To address these concerns, NCI supports development of several research resources and makes them available to the extramural research community for use in investigator-initiated research projects and NCI-supported programs. Such resources include the Human Cancer Models Initiative (HCMI)[60] and the NCI Patient-Derived Models Repository

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[58] https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/patient-engagement.

[59] https://www.cms.gov/newsroom/press-releases/cms-finalizes-coverage-next-generation-sequencing-tests-ensuring-enhanced-access-cancer-patients.

[60] https://ocg.cancer.gov/programs/HCMI.

(PDMR).[61] Many of NCI's resources are catalogued on the Resources for Researchers[62] website which provides information on how to obtain the resources.

The HCMI is a collaborative international consortium that is generating 1,000 novel, next-generation, cancer models from patient tumors that are clinically and molecularly characterized. HCMI-developed models and related genomic and clinical data are available as a community resource without excessive intellectual property (IP) constraints. The NCI is contributing to the initiative by supporting four Cancer Model Development Centers (CMDCs) at the Broad Institute, Cold Spring Harbor Laboratory, Weill Cornell Medicine, and Stanford University. These cancer models will serve as valuable resource for translational cancer research and will contribute to developing innovative therapeutic strategies, identifying novel diagnostic markers, and individualizing patient treatment plans. In addition, the initiative will make resources such as protocols used for model development, SOPs, and other model-associated support available to aid the research community to generate additional models. There are currently 19 models available through the HCMI searchable catalog.[63]

The PDMR is mainatained by the Frederick National Laboratory for Cancer Research and is a national repository of patient-derived xenografts developed from patients with solid tumors. These models are clinically-annotated with molecular information available in an easily accessible database for the extramural community. Since the launch of the PDMR in early 2017, 166 public models have been developed from 163 unique patients, and new models continue to be added for cancer types already existing in the repository. Several new cancer types are now available in the PDMR collection, including some rare cancers. These new cancer models are of high value to the research community and include: several gynecologic cancers (ovarian, vaginal, carcinosarcoma, and cervical), small cell lung cancer (a subtype of lung cancer that is a rare disease), Hurthle cell neoplasm (a rare and often aggressive form of thyroid cancer), Osteosarcomas, chondrosarcoma, squamous cell skin carcinoma, Merkel cell carcinoma (a rare and aggressive form of skin cancer), mesothelioma (a rare type of lung cancer). The primary goal of this repository is to make a publicly available archive and repository of tumor samples and models that are fully characterized from a molecular and clinical perspective, and that are easily accessible to the extramural community at a very modest cost.

NCI also supports pediatric cancer cell lines and models to address key challenges in the development of new therapies for children with cancer (all childhood cancers are considered rare diseases). NCI's Preclinical Testing Consortium (PPTC)[64] develops reliable preclinical testing data for pediatric drug candidates that can be used to inform new agent prioritization decisions. The PPTC consists of a Coordinating Center and five Research Programs that perform in vivo testing of pediatric anticancer drug candidates for a particular cancer (sarcoma and renal, neuroblastoma, osteosarcoma, leukemia, and brain tumors). The PPTC collaborates with pharmaceutical companies and academic drug developers to systematically test candidate agents against well-credentialed panels of genomically characterized childhood cancer models to identify those investigational agents most likely to have clinical activity against childhood cancers. For example, in 2011, the PPTC developed a model for a subtype of pediatric low-grade astrocytoma (PLGA, a type of brain tumor) with a mutation in a gene called BRAF and identified a targeted therapy, selumetinib, for additional research. Building upon these findings, the PBTC conducted a Phase 1 trial of selumetinib.[65] In this trial, children with BRAF-mutated PLGAs responded to treatment by showing tumor shrinkage. Based on these promising findings, the trial is now in a Phase 2 expansion with results from several cohorts reported in 2017 showing that selumetinib is active for patients with two subtypes of BRAF-mutated PLGAs.[66]

Question. What is being done to ensure that childhood cancers receive appropriate levels of funding for translational research that turns basic science into new therapies?

Answer. Pediatric cancer research remains a top priority for the NCI. Each year the Institute identifies the best research opportunities to build upon the foundation of basic science, further develop the scientific understanding of genetic drivers of

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[61] https://pdmr.cancer.gov/, https://www.cancer.gov/news-events/cancer-currents-blog/2018/nci-pdmr-cancer-research-models.
[62] https://www.cancer.gov/research/resources.
[63] https://hcmi-searchable-catalog.nci.nih.gov.
[64] http://www.ncipptc.org/.
[65] https://clinicaltrials.gov/ct2/show/NCT01089101.
[66] http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15__suppl.10504.

childhood cancers, identify effective therapies, and enhance the quality of life for pediatric cancer survivors.

When considering the Institute's investments in any category of disease research, NCI does not make decisions about funding based on predetermined targets for a specific disease area or research category. Rather, NCI relies on technical and scientific peer review, in which highly trained outside investigators perform an initial review of research proposals and evaluate them on factors such as scientific merit, likelihood of success, and potential impact. Thereafter, the National Cancer Advisory Board, which includes members with pediatric oncology expertise, also conducts a review of the research proposal. NCI leadership further evaluates proposals to consider factors such as scientific novelty and overall representation of the research topic within the NCI portfolio.

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

—The Children's Oncology Group (COG),[67] part of NCI's National Clinical Trials Network (NCTN), develops and coordinates pediatric clinical trials across more than 200-member institutions. In addition to conducting late-phase clinical trials, the COG receives NCI support for the Phase 1 and Pilot Consortium,[68] which conducts early-phase trials and pilot studies to rapidly introduce new anticancer agents into pediatric care.

—The Pediatric Oncology Branch (POB)[69] in NCI's Center for Cancer Research, part of NCI's intramural research program, conducts high-risk, high-impact basic, translational, and clinical research.

—The NCI–COG Pediatric MATCH Trial,[70] launched in July 2017, tests molecularly targeted therapies in children and adolescents with advanced cancers who have few other treatment options. This nationwide trial is open to children and adolescents from 1 to 21 years of age and currently has eight treatment arms.

—Other efforts include the Pediatric Preclinical Testing Consortium (PPTC),[71] the Therapeutically Applicable Research to Generate Effective Treatments (TARGET)[72] program, the NCI Experimental Therapeutics (NExT) Program,[73] the Childhood Cancer Survivor Study (CCSS),[74] the Pediatric Provocative Questions (PQ) Program,[75] the Pediatric Brain Tumor Consortium (PBTC),[76] the Pediatric Cancer Immunotherapy Trials Network (CITN),[77] and the New Approaches to Neuroblastoma Therapy (NANT)[78] Consortium.

—The Childhood Cancer Data Initiative proposed in the President's Budget will seek to leverage existing Federal authorities to effectively and efficiently coalesce different types of data currently collected for pediatric cancer cases across the wide variety of entities that produce and maintain it. As childhood cancers represent less than 1 percent of all new cases of cancer diagnosed in the United States each year, NCI recognizes the need to study the basic biology of pediatric cancers to develop relevant preclinical models and support clinical trials that are accessible to every child with cancer. Furthermore, it is critical that the data garnered from these studies is aggregated and appropriately shared. In addition, the integration of longitudinal data from pediatric cancer patients into adulthood, and the ability to compare adult and pediatric data broadly will have a profound impact upon our understanding of the etiology of cancer and our ability to advance research that can lead to new and better treatments.

For decades, the foundations of both childhood and adult cancer treatment were surgery, chemotherapy, and radiation therapy. Recently, immunotherapy, in which a patient's own immune system is harnessed to fight cancer, has emerged as a new pillar of cancer treatment. While some immunotherapy approaches have been effective in treating certain pediatric cancers, many immunotherapy treatments being developed for adult cancers will likely not be applicable to childhood cancers. Therefore, this area remains a critical research focus.

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[67] https://www.childrensoncologygroup.org/.
[68] https://www.childrensoncologygroup.org/index.php/phase-1-home.
[69] https://ccr.cancer.gov/Pediatric-Oncology-Branch.
[70] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match.
[71] http://www.ncipptc.org/.
[72] https://ocg.cancer.gov/programs/target.
[73] https://next.cancer.gov/.
[74] https://www.cancer.gov/types/childhood-cancers/ccss.
[75] https://grants.nih.gov/grants/guide/pa-files/PAR-16-217.html.
[76] https://www.pbtc.org/.
[77] https://ctep.cancer.gov/MajorInitiatives/cancer__immunotherapy__trials__network.htm.
[78] http://www.nant.org/.

Recent clinical advances in immunotherapy include the 2017 FDA-approval of Keytruda® (pembrolizumab), a checkpoint inhibitor, for pediatric and adult patients with classical Hodgkin lymphoma that cannot be cured with existing treatments, as well as pediatric patients with solid tumors that have specific genetic features known as mismatch repair deficiency and high microsatellite instability. This approval is significant because targeting genetic characteristics, rather than where the cancer originates in the body, creates new options for patients who might otherwise not be considered candidates for a drug. NCI is now sponsoring early-phase clinical trials of pembrolizumab in children with aggressive brain tumors.

In 2017 the FDA also approved Kymriah™ (tisagenlecleucel), a chimeric antigen receptor (CAR) T-cell therapy, for children with acute lymphoblastic leukemia (ALL). This NCI-supported discovery was first published in the New England Journal of Medicine in 2014. NCI is currently sponsoring nine clinical trials of CAR T-cell therapy in pediatric patients with other types of cancer.[79]

In April 2019, selumetinib was awarded Breakthrough Designation by the FDA,[80] following Orphan Drug Designation in February 2018,[81] for treatment of neurofibromatosis type 1 (NF1), a rare pediatric disease that can cause malignant tumors. Although Breakthrough Designation does not guarantee final approval of the drug for this purpose, it is promising news for the future of this rare pediatric disease. NCI's POB led the Phase I and II trials of selumetinib, through an intramural and extramural collaboration. Early results from the phase II trial are promising—72 percent of the 50 pediatric patients between the ages of 2 and 18 enrolled in the trial are responding to the treatment. Not only are some patients seeing their tumors shrink more than 50 percent, but many patients report less pain intensity and pain interference, as well as increased strength and range of motion.[82] If this trajectory continues, selumetinib will be the first drug ever approved for this disease.

Innovative clinical trials would not be possible without the basic research conducted to understand the biological mechanisms of disease and to identify molecular targets for therapies. The NTRK family of genes is one such example. Describing the role of this family of genes was first made possible as a result of a basic science discovery in the 1980's at NCI's Frederick National Laboratory for Cancer Research by Dr. Mariano Barbacid. Dr. Barbacid was not studying pediatric cancers, or any particular cancer type—he was on the hunt for unique genetic drivers of cancer, called oncogenes. At the time, he could not have anticipated that his discovery would eventually lead to an effective therapy for rare cancers diagnosed in children and adults.

This discovery led to the development of an NTRK inhibitor, LOXO–101 or larotrectinib, which works against unique fusion oncoproteins that drive certain pediatric and adult cancers. In May 2018, FDA issued larotrectinib an orphan drug status and Priority Review, and in November 2018, FDA granted accelerated approval to larotrectinib. This is the second FDA approval for a precision cancer therapy that is based on a particular genetic alteration, rather than the site in the body in which a cancer occurs. Larotrectinib was evaluated in both the NCI adult and pediatric MATCH phase II clinical trials.

Investigators are hopeful that the story of crizotinib (Xalkori) will be similar. Crizotinib was first developed to target a protein produced by the oncogene MET but was later found to inhibit cancer-causing forms of the ALK gene, found in anaplastic large cell lymphomas (ALCL), certain neuroblastomas, and some non-small cell lung cancers (NSCLC). ALCL and neuroblastoma both occur in pediatric patients; the connection between ALCL and ALK was established in 1994, while the identification of ALK as a driver of neuroblastoma occurred in 2008. Crizotinib was first approved for NSCLC in March 2016, and it is part of the NCI adult and pediatric MATCH trials. In 2018, the FDA granted breakthrough approval of the drug for ALCL, and COG launched a phase III trial with crizotinib in combination with chemotherapy for high-risk neuroblastoma patients.

NCI will continue to support basic, translational, and clinical research to help develop new and less toxic therapies for children with cancer. NCI is also committed to supporting cancer survivorship research to better understand and develop inter-

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[79] https://clinicaltrials.gov/ct2/results?cond=&term=CAR+T-cell&type=&rslt= &recrs=b&recrs=a&recrs=f&recrs=d&age__v=&age=0&gndr=&intr=&titles=&outc=&spons=National+Cancer+Institute&lead=&id=&cntry=&state=&city=&dist=&locn=&strd__s=&strd__e=&prcd__s=&prcd__e=&sfpd__s=&sfpd__e=&lupd__s=&lupd__e=&sort=.

[80] https://ccr.cancer.gov/news/article/mek-inhibitor-selumetinib-granted-breakthrough-designation-by-fda-to-treat-neurofibromatosis-type-one-in-pediatric-patient.

[81] https://ccr.cancer.gov/news/article/fda-grants-orphan-drug-status-to-selumetinib-for-neurofibromatosis-type-1-nf1-treatment.

[82] https://meetinglibrary.asco.org/record/159508/abstract.

ventions to address the late effects of cancer and its treatment in childhood, and adolescent and young adult (AYA) cancer survivors. NCI is currently implementing new research efforts in this area and is also supporting efforts to enhance biospecimen collection and biobanking efforts with an emphasis on pediatric cancer types and subtypes for which treatments have been least effective. Both activities are aligned with provisions of the Childhood Cancer STAR Act directed toward NCI.

Question. What is being done to ensure that SBIR funding is addressing the critical translational gap for these neglected rare cancer patients?

Answer. Consistent with the statutory mandate established by Congress, the NCI SBIR/STTR program is one of the largest sources of early stage technology financing in the United States. The program supports a diverse portfolio of research, from projects focused specifically on evaluating new treatments for rare cancers, to the development of cross-cutting technologies that enable research across cancer types. The NCI SBIR/STTR program does not direct funding based upon cancer type or research area. Funding is awarded through a rigorous and competitive peer review process, to identify the most promising research applications. NCI, including the SBIR/STTR program, recognize that there is a clear need to develop more effective treatments for many rare cancers and rare cancer subtypes that are refractory to currently available treatment options.

Examples of current SBIR projects focusing on translational and clinical research for rare cancers include:

—In 2018, NCI awarded a SBIR Phase IIB Bridge Award to Oncoceutics, Inc., which seeks to develop a new cancer drug, ONC201, for patients who have been diagnosed with recurrent glioblastoma and high-grade glioma with limited treatment options and very poor prognoses, including a pediatric high-grade glioma called Diffuse Intrinsic Pontine Glioma (DIPG).[83] Approximately 200–300 children are diagnosed with DIPG each year in the U.S., and the median survival time from diagnosis is less than 1 year.

—In 2018, NCI supported PEEL Therapeutics with an STTR award focused on pre-clinical evaluation of a novel potential therapy for osteosarcoma, a deadly pediatric bone tumor. The project is led by Dr. Josh Schiffman, who is also a researcher at the Huntsman Cancer Institute at the University of Utah.[84]

—In fiscal year 2018, NCI also funded a Phase I clinical trial of a novel first-in-class drug combination of two agents (IV fenretinide + IV safingol) through an SBIR Fast-Track Phase I/II award to CerRx, Inc. This trial, conducted at the South Plains Oncology Consortium based at the Texas Tech University Health Sciences Center, is testing for the treatment of multiple relapsed rare cancer types including Non-Hodgkin's Lymphoma, Peripheral T-Cell Lymphoma, and Esophageal Adenocarcinoma. If successful, this novel biochemistry may constitute a broad-based widely active treatment option for both adult and pediatric malignancies.[85]

While these are all important examples of research underway to support development of new therapies for rare cancers, the SBIR Program's investment in cross-cutting technologies and tools is equally important to progress in this field. A notable example of this is NCI's support of Illumina, Inc. With support from NCI's SBIR program and its Innovative Molecular Analysis Technologies (IMAT) program,[86] Illumina developed the base technology for the Infinium assay for genotyping, which is being used in the NIH All of Us Research Program, in other basic and clinical research, as well as by commercial companies like 23andMe and Ancestry.com.[87] In collaboration with NCI's SBIR/STTR program, the IMAT program is another opportunity for small businesses to pursue NCI support. IMAT aims to support the development and dissemination of novel and potentially transformative next-generation technologies, and uses a variety of investigator-initiated research project grant mechanisms to support cross-cutting, research-enabling disciplines.

These SBIR and IMAT examples, along with other NCI research efforts described in this response, represent important steps NCI is taking to support basic, translation, and clinical research to make progress for patients with rare cancers. NCI encourages small businesses interested in pursuing NCI funding to consider oppor-

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[83] https://projectreporter.nih.gov/project__info__description.cfm?aid=9524880&icde=44259659&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=.

[84] https://projectreporter.nih.gov/project__info__description.cfm?aid=9559358&icde=44276787.

[85] https://projectreporter.nih.gov/project__info__description.cfm?aid=9485913&icde=44283562.

[86] https://imat.cancer.gov/, https://imat.cancer.gov/about-imat/outputs-and-achievements/individual-technologies-and-platforms/sentrix%C2%AE-beadchip-and.

[87] https://www.cancer.gov/news-events/cancer-currents-blog/2019/nci-sbir-working-with-small-business.

tunities to apply for SBIR/STTR[88] and IMAT support,[89] as well as support through the NExT program,[90] also highlighted in this response.

Question. What is being doing to ensure that all forms of cancer have significant dataset presence in publicly available data repositories?

Answer. There are several data resources available from NCI that serve as data repositories for all forms of cancers, including rare cancers. Examples include the Genomic Data Commons (GDC) and the NCTN Navigator. The GDC[91] is a data portal that serves as a centralized location to integrate and store the diverse datasets from NCI programs. The GDC includes cancer genomic data from over 32,000 cancer cases. All GDC data is available to qualified researchers free of charge and includes data from The Cancer Genomic Atlas (TCGA),[92] where about one-third of cancer types within the TCGA resource are rare cancers; Therapeutically Applicable Research to Generate Effective Treatments (TARGET), where all of the cancers included in this pediatric genomics resource are considered rare; The Clinical Trials Sequencing Program (CTSP); and the Exceptional Responders Initiative. The GDC will also include data from future NCI Center for Cancer Genomics-sponsored cancer research programs.

Finally, the proposed fiscal year 2020 Childhood Cancer Data Initiative seeks to create a federated data system for pediatric cancer research to increase the number of cases represented, and all pediatric cancers are considered rare diseases. The data federation will include clinical records, genomic information, pathology and outcomes data and will build upon existing initiatives at NIH and NCI including the GDC and TARGET.

CANCER RESEARCH AND THE DEADLIEST CANCERS

Question. While Congress has been providing the NIH, including the National Cancer Institute, with more funding each of the past 4 years, the odds of securing a grant from NCI have actually been getting more difficult.

(A) What's driving this trend, what's its significance, and do you expect it to continue?

(B) How much of the progress that you're seeing is occurring in NCI Cancer Centers and Translational Research centers, is it disproportionate, and what accounts for their success?

(C) While the progress in cancer research is very encouraging, it remains elusive for those like cancers of the pancreas, esophagus, ovary and stomach, where progress remains elusive. What is NCI doing to address that?

Please provide the number of grants and total grant funding devoted to research related to cancers of the pancreas, esophagus, ovary, liver, brain, lung and stomach for each year from fiscal year 2013 to fiscal year 2018.

Answer. NIH appreciates the additional resources Congress provided NCI each of the past 6 years (Fiscal Years 2013–2018) to support cancer research. As members are fully aware, cancer continues to be a leading cause of death and disability for the Nation, and thus scientists around the country are motivated to find strategies for combatting the issue. The additional funding resulted in an approximately 24 percent increase to NCI's appropriation to support essential research into understanding and treating what we now recognize as a multitude of cancer subtypes. Over that same period, NCI received a nearly 50 percent increase in the number of investigator-initiated grant applications (R01s) indicating that the field continues to attract researchers to propose novel scientific proposals. Specifically, during fiscal year 2013, NCI received 4,175 investigator-initiated R01 applications. During fiscal year 2018 NCI received 6,113 R01 investigator-initiated applications, and experienced year-to-year annual growth in the number of applications throughout the period. We have also observed that the increases represent a growing number of unique investigators applying for awards, and only a small portion (approximately 10 percent) of the increase in applications is driven by individual investigators submitting multiple applications As a result, even during an era of significant budget increases, this dramatic growth in applications had increased competition for NCI funding, and NCI is taking affirmative steps to improve the chances for applicants to be funded. Of note, in fiscal year 2019, NCI expects to increase the investigator-

[88] https://sbir.cancer.gov/funding.
[89] https://imat.cancer.gov/funding-opportunities.
[90] https://next.cancer.gov/entryToPipeline/default.htm.
[91] https://gdc.cancer.gov/.
[92] Rare cancer types within TCGA are: mesothelioma, adrenal gland tumors, testicular germ cell cancer, uveal melanoma, adrenocortical carcinoma, cholangiocarinoma, chromophobe kidney cancer, adult soft tissue sarcomas, thymomas, and uterine carcinosarcoma.

initiated research grant pool by $100 million, an amount that is greater than the increase NCI received to its fiscal year 2019 base appropriation.

(A) Regarding the increase in applications to NCI, we suspect that the public health burden in combination with the scientific opportunity is the likely source of a surging biomedical research workforce in this area. We are reaping the benefits of decades of investment in basic science and rapid advances in technology that have resulted in a record number of oncology drug approvals. This includes significant progress in the development of cancer immunotherapies and molecularly targeted therapies. At the same time, we are making gains in cancer prevention and survivorship. Taking these advances into consideration with the increasingly interdisciplinary nature of cancer research, that is the intersection of genomics, data science, biology, and more, this progress continues to attract more interest and talent to the cancer research enterprise.

(B) The 70 NCI-designated Cancer Centers serve as anchors of the United States cancer research enterprise, convening concentrations of expertise that are vital to rapidly advance progress against cancer. NCI strives to provide opportunities to participate in cutting edge, NCI-supported research to every patient across the country, not just those with easy access to an NCI-designated Cancer Center and thus two additional pillars of the NCI research infrastructure are the National Clinical Trials Network (NCTN) and the NCI Community Oncology Research Program (NCORP), which seek to enroll diverse patient populations from across the Nation in NCI-sponsored research.

The NCTN is a collection of organizations and clinicians that coordinates and supports cancer clinical trials at more than 3,000 sites across the U.S. and Canada. The NCTN provides the infrastructure for NCI-funded treatment, screening, and diagnosis trials, centralizing many administrative efforts to rapidly facilitate easier enrollment of patients in clinical trials. For physicians and their patients, a variety of significant, innovative trials are widely available throughout the country, in large and small communities alike.[93]

NCORP, which works closely with the NCTN, expands NCI's reach even further. In addition to designing and conducting cancer prevention, supportive care and symptom management, screening, and surveillance clinical trials, NCORP sites recruit patients and participants to NCI-supported treatment and imaging trials, most of which are conducted through the NCTN. NCORP is led by 7 research bases and 46 community sites, and there are over 900 NCORP component sites across the country. The sites represent collaborations between researchers, public hospitals, physician practices, academic medical centers, and other groups that provide healthcare services.[94]

Independent investigators fill out the robust research infrastructure supported by NCI. This includes principal investigators for NCI's Specialized Programs of Research Excellence (SPOREs),[95] which represent collaborative translational research projects focusing on more than twenty organ sites, systems, and pathway-specific themes. While large programs like NCI-designated cancer centers, clinical trials networks, data commons, and biorepositories constitute the backbone of the cancer research enterprise, the majority of research proposals received and funded by NCI are investigator-initiated, meaning that the studies are developed by researchers themselves. This process allows for the scientific ingenuity and intellectual autonomy that is essential to advance biomedical research. In fiscal year 2018, NCI supported research at more than 700 institutions across the United States.

(C) NCI is committed to making progress against all cancers, including those that have proved most difficult to treat. Indeed, recognizing that the incentives that encourage private industry investment in therapies for more common cancers do not exist for cancers that occur less frequently, NCI has a responsibility to encourage and support research on these diseases, and does this through a variety of mechanisms, including support for disease-specific steering groups and the convening of scientific meetings and relevant cross-cutting research areas that seek to identify new scientific directions and opportunities.

One way in which NCI encourages scientific collaboration and interdisciplinary research on these disease areas is through the SPOREs program, mentioned above. These programs include basic and clinical/applied scientists working together to support projects that will result in new and diverse approaches to the prevent, detect, diagnose, and treat cancer. NCI currently supports SPOREs focused on pancreas, esophagus, ovary, liver, brain, lung and stomach cancers through the following awards:

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[93] https://www.cancer.gov/research/areas/clinical-trials/nctn.
[94] https://ncorp.cancer.gov/about/.
[95] https://trp.cancer.gov/.

—Pancreatic SPOREs are located at the Mayo Clinic, University of Nebraska Medical Center, and Washington University in St. Louis.[96]
—Gastrointestinal SPOREs, which include research on cancers of the esophagus and stomach, are located at Case Western Reserve University, Dana-Farber Harvard Cancer Institute, Johns Hopkins University, and Vanderbilt University.[97]
—Ovarian SPOREs are located at Johns Hopkins University, the Mayo Clinic, Roswell Park Cancer Institute, and University of TX/MD Anderson.[98]
—A hepatobiliary (liver) cancer SPORE is located at the Mayo Clinic.[99]
—Brain SPOREs are located at Dana-Farber Harvard Cancer Institute, Duke University Medical Center, Northwestern University at Chicago, University of California, Los Angeles, University of California, San Francisco, and University of Texas/MD Anderson.[100]
—Lung SPOREs are located at the University of Colorado Cancer Center, University of Texas/Southwestern Medicine, and Yale University.[101]

Between June 2017 and May 2018, the FDA approved several therapies for cancers that are the focus of SPORE research, advances made possible through NCI or NIH-supported research.[102] The approved treatments include:[103]

—Rucaparib (Rubrical), a maintenance treatment for recurrent ovarian, fallopian tube, or primary peritoneal cancers;
—Lutetium Lu 177 Dotatate (Lutathera) for gastroenteropancreatic neuroendocrine tumors;
—Trastuzumab-DKST (Ogivri), a biosimilar, to treat patients with certain types of metastatic stomach cancer and breast cancer;
—Pembrolizumab (Keytruda) for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express a certain biomarker;
—Olaparib tablets (Lynparza) for maintenance treatment of patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer who responded to certain chemotherapies; and
—Several approvals to treat various subtypes of non-small cell lung cancer (NSCLC):
  —Osimertinib (Tagrisso)
  —Durvalumab (Imfinzi)
  —Alectinib (Alecensa)
  —Dabrafenib (Tafinlar), in combination with Trametinib (Mekinist)

As these approvals indicate, the scientific community recognizes that within each type of cancer, there are unique subtypes, and when possible, physicians should rely on genetic and molecular markers to guide treatment. NCI's investments in basic research—understanding the underlying mechanisms that give rise to cancer—enable rapid advances of precision medicine in cancer treatment. Investigators are continuing to identify disease subtypes, which often uncovers tumors with similar genetic profiles that occur in various sites throughout the body. Such advances led to the FDA approval of FoundationOne CDX Next Generation Sequencing, a genetic test to detect alterations in 324 genes and two genomic signatures in any solid tumor type.[104] These developments benefit all cancer patients, including those with difficult to treat cancers.

Precision medicine is the foundation for the NCI MATCH (Molecular Analysis for Therapy Choice) Trial, a precision medicine trial that is expected to provide new research ideas to advance treatments in all cancer types.[105] This study is analyzing patients' tumors to determine whether they contain gene abnormalities for which a targeted drug exists, and with that information, the study assigns treatment based on the genetic abnormality. As of April 2019, 443 pancreatic cancer patients, 235 gastroesophageal cancer patients, 666 ovarian cancer patients, and 345 liver and hepatobiliary cancer patients, 131 patients with brain and other central nervous

[96] https://trp.cancer.gov/spores/pancreatic.htm.
[97] https://trp.cancer.gov/spores/gi.htm.
[98] https://trp.cancer.gov/spores/ovarian.htm.
[99] https://trp.cancer.gov/spores/hepatobiliary.htm.
[100] https://trp.cancer.gov/spores/brain.htm.
[101] https://trp.cancer.gov/spores/lung.htm.
[102] https://www.ncbi.nlm.nih.gov/pubmed/29440428.
[103] https://www.ascopost.com/issues/june-3-2018-narratives-special-issue/fda-oncology-drug-approvals-granted-between-june-2017-and-may-16-2018/.
[104] https://www.ascopost.com/issues/june-3-2018-narratives-special-issue/fda-oncology-drug-approvals-granted-between-june-2017-and-may-16-2018/.
[105] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.

system tumors, and 707 patients with various types of lung cancers have been screened for this trial.

Patients who are not assigned to an NCI MATCH treatment arm may be eligible for the NCI DART, or the Dual Anti-CTLA–4 & Anti-PD–1 blockade in Rare Tumors Trial. This study will also assess whether their tumors respond to two cutting-edge immunotherapy agents. DART is the first federally funded immunotherapy trial devoted entirely to rare cancers.[106]

As this background demonstrates, NCI will continue to support research on cancers of the pancreas, esophagus, ovary, liver, brain, lung and stomach through multiple research mechanisms.

Question. Please provide the number of grants and total grant funding devoted to research related to cancers of the pancreas, esophagus, ovary, liver, brain, lung and stomach for each year from fiscal year 2013 to fiscal year 2018.

Answer. The information requested is provided in the tables below (Table 1—Fiscal Year 2018–2016 and Table 2—Fiscal Year 2015–2013). Brain cancer, liver cancer, lung cancer, ovarian cancer and pancreatic cancer are Research, Condition, and Disease Categories (RCDC) and the data provided include the total number of projects—grants (including subprojects and supplements), contracts, and intramural research—for the NIH for those cancer types. Total funding is broken out as total NIH and total NCI funding. The data are publicly available and can be found at: https://report.nih.gov/categorical__spending.aspx.

Additionally, it is important to clarify that RCDC category listings are not budget line items. The category represents a list of projects selected for funding following the rigorous NIH peer review process. Each category list provides a look back at projects funded in a given fiscal year. NIH does not allocate funding prospectively by category, and the RCDC categories do not add up to the total NIH budget because projects can be applicable to more than one category, and categories are by their nature overlapping (e.g., neurosciences and brain cancer). RCDC is not intended to account for the entire NIH budget across thousands of research topics. More information is available on the RCDC FAQ page: https://report.nih.gov/rcdc/faqs.aspx#q18.

Esophageal cancer and stomach cancer are not currently RCDC categories. Therefore, the data provided for those sites are estimated based on NCI data for grants and intramural research projects. Although every attempt was made to provide data that is closely matched to the method used to assemble RCDC data for the other cancer sites. However, it is not comparable because there are no esophageal or stomach cancer RCDC categories.

[The information follows:]

Table 1 – FY 2018-16 funding (in millions) and number of projects

	FY 2018				FY 2017				FY 2016			
	RCDC Data[1]											
	NIH		NCI[2]		NIH		NCI		NIH		NCI	
Cancer	$[3]	Projects[4]	$	Projects	$	Projects	$	Projects	$	Projects	$	Projects
Brain	$360	953	$265	684	$332	834	$245	596	$310	789	$227	553
Liver	$113	309	$88	238	$90	231	$67	166	$83	229	$61	163
Lung	$403	1094	$354	974	$352	829	$315	737	$331	797	$291	697
Ovarian	$159	376	$142	332	$151	336	$134	293	$144	319	$126	279
Pancreatic	$215	586	$186	521	$199	498	$177	441	$168	491	$146	436
	NCI Estimated Data[5]											
			$	Projects			$	Projects			$	Projects
Esophageal			$39	94			$42	91			$37	84
Stomach			$25	59			$19	59			$17	50

[1] Data available at: https://report.nih.gov/categorical_spending.aspx

[2] NCI funds and projects are a subset of the NIH data

[3] Funding provided as millions of dollars

[4] Projects include grants, contracts and intramural research

[5] Data provided is estimated based on NCI data. Please see the response to the question for a more complete explanation.

[106] https://www.swog.org/sites/default/files/docs/2017-11/DARTrelease.pdf.

Table 2 – FY 2015-13 funding (in millions) and number of projects

	FY 2015				FY 2014[1]				FY 2013[2]			
	RCDC Data[3]											
	NIH		NCI[4]		NIH		NCI		NIH		NCI	
Cancer	$[5]	Projects[6]	$	Projects	$	Projects	$	Projects	$	Projects	$	Projects
Brain	$298	768	$226	555	$289				$280			
Liver	$85	237	$62	175	$74				$71			
Lung	$349	785	$308	687	$254				$208			
Ovarian	$118	291	$110	265	$131				$133			
Pancreatic	$174	450	$159	409	$123				$125			
	NCI Estimated Data[7]											
			$	Projects			$	Projects			$	Projects
Esophageal			$38	87			$47	81			$47	85
Stomach			$15	47			$14	50			$15	56

[1&2] For FY 2014 and FY 2013 only the total NIH funding amount is available in RCDC

[3]Data available at: https://report.nih.gov/categorical_spending.aspx

[4] NCI funds and projects are a subset of the NIH data

[5] Funding provided as millions of dollars

[6] Projects include grants, contracts and intramural research

[7] Data provided is estimated based on NCI data. Please see the response to the question for a more complete explanation.

DOWN SYNDROME AND THE INCLUDE PROJECT

Question. As a part of the INCLUDE Project, NIH has hosted scientific workshops to solicit input from the Down syndrome community on research between Alzheimer's disease and Down syndrome. What other topics does NIH plan to cover in future workshops and how will NIH plan to engage the Down syndrome community to ensure their robust participation in these workshops?

Answer. The new, trans-NIH effort, Investigating Co-occurring conditions across the Lifespan to Understand Down syndrome, or INCLUDE, was launched in summer 2018. As a key component of the INCLUDE project, the NIA is supplementing an Alzheimer's clinical trials network to include adults with Down syndrome to learn more about the development of commonly co-occurring conditions in individuals with Down syndrome that are also seen in the general population, such as dementia and Alzheimer's disease. In addition, working through its established Pediatric Trials Network, in fiscal year 2019 (NICHD will create a new pediatric clinical trials infrastructure for Down syndrome. Such a resource will also ensure that new therapies can be brought to trial as they emerge in the future. To bolster these efforts, NIH is planning two major scientific workshops within the year to address the development of a cohort in Down syndrome, and how to include people with Down syndrome in clinical trials. These efforts can take advantage of the research registry for Down syndrome, DS-Connect®,[107] a Web-based health registry that serves as a national health resource for people with Down syndrome and their families, researchers, and healthcare providers. Funded by NICHD since 2013, with over 4,400 participants, the registry facilitates information sharing about research and upcoming trials for individuals with Down syndrome, their families, and researchers.

Question. How is NIH going to use the INCLUDE Project and other investments in Down syndrome research to support the pipeline of early investigators in this field?

Answer. One of the immediate successes of INCLUDE was to attract new researchers and talent into the field. In fact, many of the recipients of awards in fiscal year 2018 were investigators who had not previously had a research focus on Down syndrome. Since the purpose of the INCLUDE project is to investigate conditions that affect both individuals with Down syndrome and the general population, researchers with subject matter expertise other than Down syndrome now have the opportunity to submit applications in response respond to one of INCLUDE's three major components: to conduct targeted, high-risk, high-reward basic science studies on chromosome 21; assemble large study populations (cohorts) of individuals with Down syndrome; and include individuals with Down syndrome in new and existing

[107] https://dsconnect.nih.gov/.

clinical trials. These opportunities are widely disseminated across the Down syndrome community through the public-private Down Syndrome Consortium that includes the Trans-NIH Working Group, 16 national and international organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members. The consortium also works toward implementing the NIH Research Plan on Down Syndrome,[108] which set research goals for Down syndrome.

In addition, NIH continues to fund from its baseline a wide range of research related to Down syndrome, across many of the NIH institutes and centers, nearly tripling its total funding for Down syndrome-related research over the last few years. For example, NICHD is funding an early-stage investigator studying children with Down syndrome, to develop outcome measures for early childhood communication. In the future, we anticipate initiatives that will be focused on support for trainees to continue to build a pipeline of investigators studying Down syndrome.

Question. People with Down syndrome have a unique disease spectrum that offers many opportunities for research. As the NIH works to set up a clinical trials network as a part of the INCLUDE Project, how do you plan to work with the Down syndrome community to encourage people with this condition to participate in clinical trials?

Answer. Over the coming year, NICHD plans to work with NIA and other partners to coordinate building an infrastructure for a clinical trials network in Down syndrome across the lifespan. At the same time, full inclusion of individuals with Down syndrome into ongoing clinical studies that have been enrolling people without Down syndrome will ensure that they will reap the benefits of therapeutic agents already in development. Working through its established Pediatric Trials Network that has enrolled over 7,000 children, in fiscal year 2019 NICHD will create a new pediatric clinical trials infrastructure for Down syndrome. This resource will also ensure that new therapies can be brought to trial quickly and efficiently as they emerge in the future. In parallel, NICHD will create and fund a training program, working with its pediatric trials experts, as well as specialists in Down syndrome, to help teach investigators how to recruit and work with individuals with Down syndrome and their families.

Further, through the INCLUDE project, NIA is supplementing an Alzheimer's clinical trials network to include adults with Down syndrome to learn more about the development of dementia and Alzheimer's disease. To bolster these efforts, NIH is planning two major scientific workshops within the year to address the development of a cohort in Down syndrome, and how to include people with Down syndrome in clinical trials. These efforts will take advantage of the research registry for Down syndrome, DS-Connect®,[109] a Web-based health registry that serves as a national health resource for people with Down syndrome and their families, researchers, and healthcare providers. Funded by NICHD since 2013, the registry facilitates information sharing about research and upcoming studies for both individuals with Down syndrome and researchers.

Question. We are pleased to see so many NIH Institutes and Centers participating in the INCLUDE Project. What kind of feedback have you been getting from the Institutes on this project, particularly as it may offer lessons learned for other trans-NIH initiatives?

Answer. INCLUDE involves research projects or programs funded by 14 NIH Institutes and Centers. INCLUDE will investigate conditions that affect both individuals with Down syndrome and the general population, such as Alzheimer's disease/dementia, autism, cataracts, celiac disease, congenital heart disease, and diabetes. This approach is creating new synergies among the NIH institutes and centers that study these conditions. To give just two examples from the first round of awards, NICHD is funding a project that will sequence the genomes of children with Down syndrome who also have congenital heart defects or leukemia. The results will be publicly available, allowing researchers globally to test hypotheses and find new gene variants that are associated with both Down syndrome and these additional conditions. NIA is developing a Down syndrome module for its Alzheimer's disease research centers with the goal of learning more about the development of dementia that will lead to potential treatments.

Question. I recently learned that people with Down syndrome rarely get solid tumor cancers. For example, women with Down syndrome most likely would not ever need to get a mammogram because they are highly unlikely to develop breast cancer. The connection between Down syndrome and cancer seems like a promising research opportunity. Can you tell us about some of the topics that NIH is prioritizing in the INCLUDE Project?

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[108] https://www.nichd.nih.gov/publications/product/441.
[109] https://dsconnect.nih.gov/.

Answer. NIH was grateful to have the opportunity to dedicate more resources in fiscal year 2018 toward research related to Down syndrome through the INCLUDE project. In its first year, over $22 million was spent on projects under this new initiative alone. This figure was in addition to the baseline funding of $37 million for Down syndrome for a total of approximately $60 million. Awards were made to a wide range of investigators across the country,[110] covering all aspects of the INCLUDE project: research to improve the understanding of the biology of Down syndrome, research focused on connecting large study populations (or cohorts) of individuals with Down syndrome and enrolling new participants at different ages, and identifying existing clinical trials that seek to address conditions common in individuals with Down syndrome to bolster recruitment and inclusion in more clinical studies.

INCLUDE involves research projects or programs funded by 14 NIH Institutes and Centers, investigating conditions that affect both individuals with Down syndrome and the general population, such as Alzheimer's disease/dementia, autism, cataracts, celiac disease, congenital heart disease, and diabetes. This approach is creating new synergies among the NIH institutes and centers that study these conditions. To give just two examples from the first round of awards, NICHD is funding a project that will sequence the genomes of children with Down syndrome who also have congenital heart defects or leukemia. The results will be publicly available, allowing researchers globally to test hypotheses and find new gene variants that are associated with these conditions. NIA is developing a Down syndrome module for its Alzheimer's centers with the goal of learning more about the development of dementia and lead to potential treatments.

Question. I was pleased to learn that one of the aims of the INCLUDE Project is to encourage scientists studying other topics like cancer, Alzheimer's, and autoimmune disease to add research on Down syndrome to their work. What kind of feedback have you gotten from the research community on these opportunities?

Answer. One of its immediate successes of INCLUDE was to attract new researchers and talent into the field. In fact, many of the recipients of awards in fiscal year 2018 were investigators who had not previously had a research focus on Down syndrome. Since the purpose of the INCLUDE project is to investigate conditions that affect both individuals with DS and the general population, researchers with subject matter expertise other than Down syndrome now have the opportunity to submit applications. These opportunities are widely disseminated across the Down syndrome community through the public-private Down Syndrome Consortium that includes the Trans-NIH Working Group, 16 national and international organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members. The response has been robust, demonstrating excitement among investigators who previously have not been involved in Down syndrome research.

ANTIBIOTIC RESISTANCE

Question. We have been hearing warnings for decades that overuse of antimicrobials is reducing their effectiveness, and that appears to be borne out by reports of a new superbug, Candida Auris.

Where does NIH see the greatest opportunities for medical research to provide solutions to the threat posed by antimicrobial resistance?

Answer. NIAID is the lead institute for antimicrobial resistance (AMR) research at NIH. NIAID supports a comprehensive portfolio of basic, translational, and applied research on AMR to better understand pathogenicity and the mechanisms by which resistant pathogens overcome antimicrobials, and to develop novel diagnostics, therapeutics, and vaccines. Recent advances in AMR research have created a number of scientific opportunities, particularly to: (1) accelerate the development of new antimicrobials with novel mechanisms of action; (2) identify ways to enhance or target the body's immune system to better fight infection; (3) manipulate microbial communities to prevent or treat colonization by harmful pathogens; and (4) develop state-of-the-art antivirulence strategies and rapid diagnostics to help control the spread of AMR. NIAID is pursuing these opportunities for both bacterial and fungal pathogens.

NIAID is supporting development of a number of novel antimicrobial agents, including a group of novel forms of a class of antibiotics (tetracyclines) that are not susceptible to existing resistance mechanisms in bacteria. One of these compounds, XERAVATM, recently received FDA approval to treat complicated intra-abdominal infections. NIAID funding also has led to the discovery of a new class of antibiotics, malacidins, that are being investigated for further therapeutic development. In addi-

[110] https://www.nih.gov/include-project/funding.

tion, NIAID is providing CARB–X (Combating Antibiotic Resistant Bacteria-X), a public-private partnership led by BARDA within HHS with in kind and technical support. CARB–X is currently funding 35 innovative projects—including 13 that represent new classes of antibiotics.

NIAID currently is exploring several alternatives to traditional antimicrobials that leverage advances in basic research on pathogenesis, drug resistance, immune system function, and the microbiome. NIAID-supported scientists are exploring the use of protective bacterial strains and fecal microbiota transplant to prevent and treat bacterial infections. NIAID grantees also are investigating ways to boost the ability of an individual's own immune system to fight infection. This includes the use of modified immune cells to control invasive fungal infections, and studies by NIAID investigators to boost the immune system's ability to fight the bacterial species Klebsiella pneumoniae infection using targeted antibodies. NIAID also is advancing the development of candidate vaccines against bacterial and fungal pathogens, including strains that exhibit drug resistance. One such experimental vaccine, NDV–3, exhibited protection in animal models against Staphylococcus and Candida species, including Candida auris (C. auris). NDV–3 also was shown to be safe and well-tolerated in a Phase 1 clinical study. Vaccines that confer protection against bacterial and fungal pathogens have the added benefit of mitigating the use of antimicrobial drugs and potentially avoiding the development of AMR.

NIAID also is supporting the development of novel diagnostic tools to help control the emergence and spread of drug-resistant pathogens. The NIAID Antibacterial Resistance Leadership Group (ARLG) oversees clinical research on antibiotic resistance, including antimicrobial stewardship, infection prevention, and improved diagnostics. ARLG efforts include the development of a master protocol for evaluating multiple diagnostic tests using samples from a single patient. NIAID support also has contributed to the development of several novel diagnostics capable of distinguishing between numerous infectious agents, including a sepsis diagnostic that simultaneously tests for 24 bacterial and fungal species, and a pneumonia diagnostic that can detect a number of different bacterial and viral species as well as seven genetic markers of AMR. Both diagnostics have received FDA clearance. In addition, NIH, in partnership with BARDA, is supporting the AMR Diagnostic Challenge competition. The Diagnostics Challenge aims to accelerate the development of raid, point-of-need diagnostic tests that can help inform treatment and facilitate antibiotic stewardship. Submissions for Step 3 of the Challenge are due in January 2020, and final results of the competition are anticipated in July 2020.

Question. There are already a number of superbugs like MRSA and C–R–E that pose challenges in hospitals and other healthcare settings, what is significant about Candida Auris?

Answer. Candida are fungi that can be found on the skin, mucous membranes, and in the intestinal tract. For people with certain risk factors, excessive growth of these fungi can cause invasive candidiasis—a serious infection that can affect the blood, heart, brain, eyes, bones and other parts of the body. C. auris is a newly emerging fungal species that is challenging to diagnose and is often resistant to multiple antifungal drugs. While most C. auris infections are treatable with existing antifungal drugs, the presence of C. auris infections resistant to three of the main classes of antifungal drugs is extremely concerning. In addition, C. auris is extremely difficult to eliminate from contaminated surfaces, and it can spread from person-to-person. Drug development for fungal pathogens poses an especially challenging problem. Unlike antibacterial drugs, which mostly target bacterial pathways that are very different than those in humans, many fundamental biochemical and cellular processes are similar in fungi and humans. Thus, many fungal drug candidates may pose a safety risk to humans because they could also target the similar human pathways, with potentially toxic side effects.

AMR research supported by NIAID is especially critical in light of the emergence of novel AMR pathogens such as C. auris, which exhibits a unique multidrug resistance that has not been seen in other species of Candida. A major component of NIAID-supported research on C. auris is focused on developing an improved understanding of resistance mechanisms to better inform therapeutic development efforts. This includes genomic analysis of C. auris—including isolates from two recent outbreaks—as well as efforts to better understand host-pathogen interactions and resistance mechanisms for particular antifungal drugs. NIAID also is screening antifungal compounds for in vitro effectiveness against C. auris. Of 15 compounds tested to date, 11 showed activity against C. auris. NIAID also supports studies of a broad-spectrum antifungal with activity against C. auris and other Candida species. In addition, NIAID scientists have developed animal models to study C. auris infection and to screen investigational therapeutics, three of which showed activity

against C. auris. Two of these investigational therapeutics are currently in various stages of clinical development.

Question. This is clearly a problem that goes far beyond the NIH or even the United States. How is NIH working its your other Federal and international partners?

Answer. NIAID works closely with its Federal partners, including the Centers for Disease Control and Prevention (CDC), BARDA, and FDA to monitor the spread of drug-resistant pathogens and further the development of promising diagnostics, therapeutics, and vaccines for AMR pathogens. NIAID continues to support CARB–X, the BARDA-led public-private partnership to incentivize the early development of antibiotics, vaccines, and diagnostics to combat resistance to antimicrobials that also is supported by the United Kingdom and Germany. NIAID also participates in the Transatlantic Task Force for Antimicrobial Resistance (TATFAR), which was established in 2009 with the goal of enhancing communication and cooperation in: 1) antimicrobial stewardship; 2) prevention and control of AMR; and 3) enhancement of the antimicrobial drug development pipeline. NIAID, through TATFAR, has aligned clinical trial networks with the European Union to expand access to patients in a clinical trial to optimize the antibacterial drug colistin for carbapenem-resistant Enterobacteriaceae (CRE) and in a clinical trial to evaluate an antibody for use against Pseudomonas. These collaborative efforts are helpful in gathering a sufficient number of patients to conduct critical AMR clinical studies. In addition, the NIAID-supported ARLG has established collaborations in 19 countries and has recently established a collaboration with the Combatting Bacterial Resistance in Europe (COMBACTE) consortium to enable joint design and implementation of clinical research on antibiotic resistance. NIAID will continue to build on recent progress in AMR research, including studies on C. auris, and is committed to supporting partnerships with academia, industry, and Federal and international partners to develop novel strategies to combat the spread of AMR in bacterial and fungal pathogens.

NEW KINDS OF INVESTIGATORS

Question. How have the BRAIN initiative and efforts around Alzheimer's disease helped recruit new investigators from various disciplines with diverse skill sets and backgrounds to work in these areas, and what have been the results? Is this something that could and should be replicated in other parts of NIH?

Answer. The challenge, allure, and importance of understanding the brain and its disorders have always attracted scientists and clinicians with diverse skills and backgrounds. The Brain Research through Advancing Innovative NeuroTechnologies (BRAIN) Initiative, which is advancing the frontiers of technology and of brain science, has attracted an even wider breadth of skill and talent. The Initiative has engaged the full spectrum of neuroscientists and clinicians, including neurologists, neurosurgeons, and psychiatrists, and recruited experts from disciplines that include behavior, chemistry, cell biology, mathematics, nanoscience, optics, and physics, as well as computer science and informatics. More than a quarter of researchers at the BRAIN Initiative Annual Investigators meeting this April were engineers, which reflects the strong emphasis on technology development. About a quarter of principal investigators are also early stage investigators, receiving their first independent NIH funding, and many other project leaders and members of research teams are entirely new to neuroscience.

To recruit this broad spectrum of investigators, the Initiative has emphasized the importance of diverse expertise since its inception. Funding opportunity announcements explicitly call for innovative and diverse approaches, with integration of technology developers and neuroscientists, and of theorists, computational biologists, and experimentalists. Peer review panels are attuned to this priority of the Initiative. Extensive outreach has reinforced this emphasis.

NIH has also been particularly successful in encouraging early-stage investigators as well as established investigators not previously focusing on Alzheimer's disease and related dementias (AD/ADRD) to apply for AD/ADRD-related research funding. An internal NIA analysis has shown that between 2015 and 2018, over a quarter of the Institute's Research Project Grant (R01) equivalent AD/ADRD awardees were either NIH-designated New Investigators (i.e., this was their first competitive NIH grant) or Early-Stage Investigators (not only was this their first competitive NIH grant, but they were also within 10 years of their terminal degree). Approximately one third of the R01 AD/ADRD awardees had not previously applied for AD/ADRD funding from NIH—just below half of whom were established investigators previously pursuing other lines of research. We anticipate that the success of these in-

vestigators in securing funding will ensure an active pipeline of energetic researchers looking at AD/ADRD from new perspectives for years to come.

Recognizing the importance of bringing fresh perspectives, NIA also released a notice in 2018 inviting researchers holding non-AD/ADRD grants from other NIH Institutes and Offices to apply for supplemental funding for new research that was relevant to both AD/ADRD and the topic of their research grant. The response was robust. Over 300 supplements were awarded to investigators representing some 25 NIH Institutes, Centers, and Offices, broadening the spectrum of research and inspiring investigators to think creatively about how their area of study could interface productively with research on AD/ADRD.

Although each disease and field of medicine presents unique challenges, NIH is certainly learning from Alzheimer's disease research and the BRAIN Initiative on the value of bringing in diverse expertise and new investigators and the strategies to accomplish that. Just as the Human Genome Project stimulated many areas of science and medicine beyond genetics, we expect the knowledge, technology, and strategies stimulated by the BRAIN Initiative and the aggressive goals of Alzheimer's and related dementias research will have much broader implications. NIH will continue to track progress in multi-disciplinary collaborations to ensure best practices are promulgated.

METHAMPHETAMINE TREATMENT

Question. Parts of the U.S. are seeing an alarming increase in methamphetamine overdoses over the past few years. As you know, there are currently no FDA-approved treatments for methamphetamine dependence. What can you tell me about NIDA's efforts to develop treatments methamphetamine addiction?

Answer. NIH is committed to addressing the alarming increase in methamphetamine overdoses, which rose fivefold from 1999 to 2017. As mentioned, there are currently no FDA-approved treatments for methamphetamine dependence and the most effective treatments are behavioral therapies, such as cognitive behavioral therapy and contingency management. While drug targets exist for methamphetamine that are analogous to those used in treating opioid addiction, alcohol addiction, and nicotine addiction, targeting them has not been similarly successful, necessitating a novel drug development approach.

NIH, primarily through NIDA, continues to invest in tackling methamphetamine addiction, investing roughly $49 million on methamphetamine research in fiscal year 2018. NIDA takes a multi-pronged approach to this challenge, balancing its portfolio across basic research on the health effects of use, epidemiology of use and addiction, and efforts aimed at developing new treatments. This strategy allows researchers to test promising treatments and to leverage our increasing understanding of methamphetamine's mechanism of action to devise new ones. Importantly, as part of this portfolio, NIDA supports clinical trials using a wide range of potential approaches, from targeting signaling pathways involved in building tolerance to methamphetamine, to exploring immunotherapy and anti-inflammatory approaches, to testing effective pharmacotherapies for opioid use disorder that might have potential to help in methamphetamine use.

Much of the research in this area to date has involved testing drugs that are already approved for other conditions, such as antidepressants and medications for opioid use disorder. While none of the drugs tested to date were sufficiently effective to warrant use in routine treatment, one potentially promising therapy uses antibodies that bind to methamphetamine and block it from reaching the brain, thus preventing both the euphoric effects and the brain changes that lead to addiction. NIDA is also supporting the study of behavioral interventions using mobile apps that might help individuals with methamphetamine addiction adhere to treatment and remain abstinent. While many of the trials are still in the fairly early stages, some have yielded preliminary analyses that may offer hope for patients suffering from methamphetamine dependence.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

NEW FUNDING

Question. Over the past 4 years, this Committee has provided NIH with more than $9 billion in increased funding, a 30 percent increase. Dr. Collins, what has this 30 percent increase meant to NIH? What new initiatives or projects have you been able to establish as a result of the new funding? How many new and promising grants have you been able to fund with the additional funding?

Answer. These resources have supported a broad range of research conducted both through NIH's intramural research program and through the tens of thousands of extramural researchers in institutions across the country. This truly exciting, world class science is leading to breakthroughs in multiple areas.

More than two-thirds of the NIH budget supports extramural research grants, and funding for these grants grew 33 percent over the last 4 years, slightly faster than the 30 percent overall budget increase. Funding for research project grants (RPGs), which are the classic mechanism of support for investigator-led research into specific biomedical research questions, grew by 37 percent over this period. This funding increase allowed NIH to increase the number of RPG awards, while also compensating researchers for the effects of biomedical research inflation. The total number of RPG awards grew by 7,010, or 20 percent, from fiscal year 2015 through fiscal year 2019. Meanwhile, the number of new and competing awards grew by 2,135, or 22 percent. This increase allowed the RPG success rate to rise from 18.3 percent in fiscal year 2015 to an estimated 20.3 percent in fiscal year 2019 in spite of an increase of more than 10 percent in the number of applications. Increased resources have allowed NIH to initiate or expand a number of critical research programs. The following list highlights just a few examples:[111]

—*All of Us.* Initiated in fiscal year 2016, the NIH All of Us Research Program is a historic effort to gather data from one million or more people living in the U.S. to accelerate research and improve health. All of Us, funded in part with amounts authorized by the 21st Century Cures Act, is a key element of the Precision Medicine Initiative (PMI), which seeks to take into account individual differences in lifestyle, environment, and biology to enable prevention and treatment strategies tailored to individuals. All of Us will serve as a national research resource to support thousands of studies, covering a wide variety of health conditions. As of early April 2019, more than 212,000 people had begun the enrollment process, and more than 129,000 had completed all the steps in the protocol.

—*Cancer Moonshot.* Resources authorized by the Cures Act for the Beau Biden Cancer Moonshot are catalyzing progress in a number of areas to improve diagnosis and treatment of a broad range of cancers. Investments in the rapidly advancing field of cancer immunotherapy are particularly promising in harnessing the body's own immune system to fight off the disease. Resources are also being used to create a national ecosystem for sharing and analyzing cancer data to facilitate efficient data analysis, to overcome drug resistance of cancer cells, and to minimize the debilitating side effects of some cancer treatments.

—*Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative.* The BRAIN Initiative, which is also supported in part with Cures Act funding, seeks to develop and apply technologies that will revolutionize our understanding of the human brain in health and disease. The initiative has supported research identifying the gene expression patterns of different subtypes of brain cells that can identify what makes different types of cells unique, demonstrating the use of neurotechnologies with clinical applications, such as deep brain stimulation, and mapping functional circuits across the brain, paving the way for an unprecedented level of understanding of the human brain and improving human health.

—*Helping to End Addiction Long-Term (HEAL).* The HEAL Initiative, first funded in fiscal year 2018, aims to bring scientific solutions to address the crisis of opioid addiction and to provide safe and effective options for the more than 25 million Americans who suffer from daily chronic pain. Through HEAL, NIH is building on basic science discoveries to accelerate the development of novel medications and devices to treat all aspects of the opioid addiction cycle, including chronic use, withdrawal symptoms, craving, relapse, and overdose. In addition, studies on integrating prevention and treatment approaches into practice, including the HEALing Communities study, will inform understanding of how the implementation of promising and evidence-based strategies and treatments can decrease opioid use disorder and overdose deaths.

—*Alzheimer's Disease.* Overall NIH funding for research into Alzheimer's Disease and related dementias (AD/ADRD) has grown almost threefold over the last 4 years, from $631 million in fiscal year 2015 to $2,468 million in fiscal year 2019.1 Approximately 70 funding opportunity announcements (FOAs) relating

[111] Estimates for Alzheimer's Disease and antimicrobial resistance are from NIH estimates of support for research, condition, and disease categories (RCDC), available on the NIH website at https://report.nih.gov/. These estimates show research support for 288 research, condition, and disease categories ranging alphabetically from Acquired Cognitive Impairment to Youth Violence Prevention, including project detail for completed years.

to AD/ADRD are currently active, including new clinical and preclinical studies. A new NIH-supported clinical trials consortium is expected to accelerate and expand studies for therapies in Alzheimer's Disease and related dementias. The Alzheimer's Clinical Trial Consortium (ACTC) will encompass 35 sites across the United States, and will address the timeframe, complexity and expense of the recruitment process and site activation for Alzheimer's trials to find new and effective ways to treat or prevent these devastating disorders.

—*Combatting Antimicrobial Resistance.* NIH-funded research to combat the rising public health problem of drug-resistant bacteria has nearly doubled since fiscal year 2015.1 Antibiotic resistant bacteria cause at least 2 million infections and 23,000 deaths each year in the United States, according to the CDC. These efforts include the Antimicrobial Resistance Diagnostic Challenge, a $20 million Federal prize competition seeking innovative, rapid point-of-care laboratory diagnostic tests to combat the development and spread of drug resistant bacteria. Five finalists in the competition were announced in December of 2018.

—The Challenge is a joint effort between the National Institutes of Health and the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) in support of the National Action Plan for Combating Antibiotic Resistant Bacteria. NIAID and ASPR's BARDA are each contributing $10 million to the Challenge. The Challenge also was developed with technical and regulatory expertise from the CDC, the FDA, and NIH Office of the Director.

—*Universal Flu Vaccine.* In fiscal year 2018, NIH unveiled a strategic plan to guide future basic, translational, and clinical research investments in areas essential to creating a safe and effective universal influenza vaccine. Along this path, NIH is funding basic research to understand the transmission, natural history, and disease process of influenza. Several universal flu vaccine strategies are already being tested in NIH-supported clinical trials.

—*Down Syndrome.* The INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) project, launched in fiscal year 2018, is a new trans-NIH research initiative on critical health and quality-of-life needs for individuals with Down syndrome. INCLUDE will assemble a large study population of individuals with Down syndrome and include individuals with Down syndrome in existing clinical trials. Individuals with Down syndrome are at higher risk for certain diseases such as Alzheimer's Disease, but at lower risk for others such as coronary artery disease and solid tumors, raising the possibility that better understanding Down syndrome will yield health benefits for the general population as well.

E-CIGARETTES

Question. Big Tobacco says e-cigarettes are a "safe" alternative to cigarettes, a way to get people to stop smoking. They make this claim despite never having conducted a clinical trial in the U.S. to prove it. So, while we don't actually know if e-cigarettes help adults quit, we do know that they are causing kids to start vaping and smoking. In 2018, youth use of e-cigarettes increased by 78 percent among high school students, and 48 percent among middle-school students. Today, nearly 4 million children are using e-cigarettes. This dramatic uptick is due to products like JUUL and kid-friendly flavors—fruit medley, fruity pebbles, choco milkshake, smurf, gummy bear. 81 percent of kids vaping started with a flavored product. What is even more alarming is that there's evidence to suggest that e-cigarettes are actually causing kids to start smoking cigarettes! Dr. Collins, Dr. Lowy, and Dr. Volkow, are you alarmed by what you've seen with the massive increase in youth use of e-cigarettes? Just last week, the FDA reported that some people were having seizures as a result of e-cigarette use. What do we know about the health effects of e-cigarettes, especially for children?

Answer. Any increase in nicotine use among adolescents is alarming. While youth cigarette smoking is at an all-time low, overall nicotine use through vaping is rising and reversing these gains. There is a perception that vaping is harmless because it does not involve the burning of tobacco—the source of carcinogenic tar in combustible cigarette smoke. While the long-term health impacts of e-cigarette use are unknown, emerging data from toxicological, animal, and human studies point to some concerning precursors to disease endpoints and health effects. For example:

—Chemicals that are known carcinogens—for example, formaldehyde—have been found in e-cigarette aerosol and are found in increasing amounts at higher heat levels.[112]

[112] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5954153/.

—Primary exposure to e-cigarette aerosol may increase oxidative stress and inflammation, important risk factors for cancer, cardiovascular, and pulmonary health consequences.[113] For example, earlier this year, NCI-supported researchers published findings that people who vaped were nearly twice as likely to experience wheezing compared to people who didn't regularly use tobacco products.[114]

—E-cigarette use may cause lasting changes to gene expression. Preliminary results from a study of nearly 100 e-cigarette users led by NIEHS intramural investigators suggest that e-cigarette use may cause unique patterns of DNA modifications in blood cells which could alter gene expression in these cells.

—Nicotine exposure during adolescence can cause addiction and harm the developing brain. NIDA, along with NCI, NIAAA, and other NIH Institutes and Centers, is leading the Adolescent Brain and Cognitive Development Study, which will examine the effects of environmental factors, including nicotine use, on the developing brains of adolescents.

FDA recently reported on 35 cases of seizures among people who have used e-cigarettes, including youth and young adults, between 2010 and 2019. Although seizure is a known potential consequence of nicotine poisoning, FDA cautioned that it does not know if there is a direct relationship between e-cigarette use and seizure risk, or how e-cigarette use behavior, use of other substances, or underlying conditions may have contributed to these seizures.[115] Despite those unknowns, NIH agrees with the FDA that it is important to share information on potential serious risks with the public as it becomes evident.

Several studies, some funded by an FDA–NIH partnership, demonstrate that e-cigarette use among never-smoking youth is a risk factor for future cigarette smoking.[116] One found that non-smoking youth who try e-cigarettes are more likely to use combustible tobacco products in the future than never users of e-cigarettes.[117] This is particularly worrisome considering that viewing e-cigarette advertising is associated with initiating e-cigarette use among youth,[118] and exposure to e-cigarette ads on social media sites increases the likelihood of subsequent e-cigarette use among youth who had never used e-cigarettes.[119]

Research regarding e-cigarettes and other electronic nicotine delivery systems (ENDS) (an umbrella term which includes JUUL), is of high interest to NIH. NIH recently developed and published two trans-NIH Funding Opportunity Announcements—one calling for research on the population, applied, and clinical impacts of ENDS [120] and the other on basic science studies of the health effects from ENDS.[121] NHLBI also organized a two-day meeting of scientific experts in 2015 that led to two grant solicitations, one in 2017 and one in 2018. Twenty research projects have been awarded through these programs, including animal studies on the effect of e-cigarettes on young versus old hearts,[122] the susceptibility of adolescent airways to e-cigarette exposure,[123] and the cardiopulmonary health of individuals in households where family members smoke e-cigarettes.[124] In addition, NIH is studying how prevention and cessation approaches developed for combustible cigarettes might be adapted for similar purposes in e-cigarettes. By furthering our understanding of how they are used, how they affect the body, and how we can implement strategies to prevent and reduce their use, NIH aims to find ways to reverse this alarming trend and reduce the harms associated with it.

INFANT MORTALITY

Question. Too often in our country, new moms and infants—especially women and babies of color—are dying from preventable health problems. The U.S. is one of only 13 countries where our maternal mortality rates are worse today than they were

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[113] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5768608/.
[114] https://www.ncbi.nlm.nih.gov/pubmed/30760629.
[115] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635157.htm.
[116] https://jamanetwork.com/journals/jamapediatrics/fullarticle/2634377;https://www.ncbi.nlm.nih.gov/pubmed/26348249;https://www.ncbi.nlm.nih.gov/pubmed/26811353; https://www.ncbi.nlm.nih.gov/pubmed/27296866.
[117] https://jamanetwork.com/journals/jama/fullarticle/2428954?resultClick=3,.
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[120] https://grants.nih.gov/grants/guide/pa-files/PAR-18-612.html.
[121] https://grants.nih.gov/grants/guide/pa-files/PAR-17-476.html.
[122] https://projectreporter.nih.gov/project__info__description.cfm?aid=9624711&icde=44343194&ddparam=&ddvalue=&ddsub=&cr= 1&csb=default&cs=ASC&pball=.
[123] https://projectreporter.nih.gov/project__info__description.cfm?aid=9567413&icde=44343005&ddparam=&ddvalue=&ddsub=&cr= 1&csb=default&cs=ASC&pball=.
[124] https://projectreporter.nih.gov/project__info__description.cfm?aid=9564974&icde=44342386.

25 years ago. Nationwide, more than 700 women die every year as a result of pregnancy—more than 70,000 others experience severe, near-fatal complications. In Illinois, 73 women die every year due to pregnancy-related complications—70 percent of these deaths are deemed preventable. We are also losing babies. Annually, more than 23,000 babies die in the U.S., many due to preventable factors. Education and income offer no protection—a black woman with an advanced degree is more likely to lose her baby than a white woman with less than an eighth-grade education. Dr. Collins, why is this happening in the year 2019? What research is NIH doing with respect to infant and maternal mortality, especially for women and babies of color?

Answer. NIH supports a large and diverse portfolio of research in maternal health, pregnancy and pregnancy outcomes, and infant mortality, including stillbirth and Sudden Infant Death Syndrome (SIDS). For example, in fiscal year 2018, NIH funded approximately $303 million on research related to maternal health.[125] The NICHD is holding a number of workshops aimed at looking at the high rate of maternal mortality in the U.S., with a focus on the factors that are contributing to maternal deaths in black women. The first, in April 2019, was a forum for members of community-based and healthcare provider groups about community engagement strategies to improve maternal health. Participants learned how patient-provider interactions and the process for making clinical care decisions affect maternal healthcare experiences at the local level. The second workshop, to be held May 2019, will bring scientific experts together to discuss research needed to address maternal mortality in the U.S. Participants will examine data quality and trends, the populations disproportionately affected, social determinants of maternal mortality, and clinical causes of this serious public health issue. Among the issues to be discussed are potential causes of the disparities in maternal mortality, such as medical mistrust, neighborhood environment, and the cultural frameworks needed to improve maternal health outcomes. A third workshop, to be held in early 2020, will focus on research needed by the medical community to address maternal mortality due to co-morbid conditions such as obesity, hypertension and diabetes, conditions prevalent in black women. Finally, as requested by Congress, NICHD has also contracted with the National Academies of Sciences, Engineering, and Medicine to conduct a study on the choice of birth setting, including risk factors, social determinants that influence risk, and maternal health outcomes.

In the meantime, NICHD continues to fund investigator-initiated prevention research on the factors that promote healthy pregnancy, e.g., weight gain in pregnancy, lifestyle interventions, and efforts to reduce exposure of pregnant women to risk factors. For example, a recent NICHD-funded study showed that health outcomes associated with short interpregnancy intervals vary by age. Compared to younger mothers, mothers over 35 are at higher risk of death and serious illness if they conceive 6 months or less after the birth of a previous child.

NICHD also supports a range of research projects related to pregnancy loss and other adverse pregnancy outcomes, determinants (e.g., biomarkers) of healthy pregnancies, and disparities among racial and ethnic groups and geographic regions. Among NICHD's research priorities are the development of specific algorithms that include physiological, biochemical, and genetic markers to predict pregnant women at risk for pregnancy loss and/or stillbirth, improving the chances for intervention. One NICHD-supported study published in 2018 found that, in an animal model, Zika virus infection caused early loss of one-quarter of the pregnancies. Unfortunately, many causes of pregnancy loss are still unknown and could result from chromosomal factors, problems with the placenta, fetal infection, and maternal disorders. Environmental exposures also may influence pregnancy loss. For example, population-based research conducted in NICHD's intramural division found that excessive exposure to high ozone levels during the last week of pregnancy, and exposures to extremes in temperature, increased the risk of stillbirths.

NICHD has a longstanding program of research on newborn screening, part of the highly successful, nationwide newborn screening public health effort that allows infants with serious or even fatal conditions to be identified for early treatment. The research component, The Hunter Kelly Newborn Screening Research Program, was originally established as a provision of The Newborn Screening Saves Lives Act of 2007. Research under the program, led by NICHD, focuses on identifying, developing, and testing new newborn screening technologies in order to improve existing tests and develop new tests, and developing and testing innovative interventions and treatments for conditions that can be detected through screening, but which are not yet treatable. In the past year, a NICHD-funded study developed a newborn screening tool to detect Niemann-Pick Disease, a rare but fatal disorder. Niemann-

[125] https://report.nih.gov/categorical__spending__project__listing.aspx?FY=2018&ARRA=N&DCat=Maternal Health.

Pick disease type C (NPC) is a rare but fatal disorder that is caused by defects in how the body stores cholesterol. Because NPC symptoms vary widely, the disease often goes undetected, causing the brain and body to degenerate beyond the point of treatment. NICHD-supported researchers found that one bile acid is increased 101-fold in patients with NPC, and quickly developed a method to detect this bile acid in dried blood spots; the method helps to detect Niemann-Pick disease in patients after birth, allowing doctors to treat them as soon as possible.

In the meantime, NICHD continues to fund research to uncover the causes of SIDS. Among the many research grants that NICHD recently funded are hippocampus and brain stem studies in SIDS infants, cardiac channel mutations, and respiratory and autonomic mechanisms potentially underlying SIDS. In addition, NICHD's leadership of the Safe to Sleep® public education campaign, working with its many collaborators, allows us to translate scientific findings on Sudden Unexpected Infant Death and Sudden Infant Deaths Syndrome (SUID–SIDS) into audience-tailored actionable messages. These efforts provide training, education, and support for parents and families, healthcare providers, and other infant caregivers in applying safe infant sleep practices. We collaborate closely with our Federal HHS partners to ensure consistent public communication. NICHD also supports focused activities with health departments in areas with high SUID–SIDS rates to train service providers and community leaders on effective risk-reduction practices and outreach tactics. For instance, one currently funded grant is exploring ways of enhancing safe sleep practices of urban low-income mothers.

BIG PHARMA

Question. All 210 drugs approved by the Food and Drug Administration (FDA) between 2010 and 2016 received NIH funding. But today, Americans are being hit twice by Big Pharma—we pay the highest prices in the world for many drugs, and we fund the development of them in the first place, mostly from NIH. On top of that, drug companies exploit another government-granted reward, the patent system. Two of the costliest cancer drugs are Rituxan and Revlimid. Both were developed with NIH funding, and both have received over 40 years of monopoly protection—because both of these medications has been issued more than 94 patents. The top 12 best-selling drugs in the United States each have an average of 71 patents, and their prices have increased by an average of 70 percent over the last 5 years. In fact, 74 percent of all new drug patents are for drugs already on the market—extending monopolies well-past the 20-year patent term. In fiscal year 2017, the NIH executed 328 licensing agreements to transfer government- and taxpayer-funded intellectual property to industry to bring these inventions to market. Dr. Collins, do you believe drug companies are abusing the patent system? Do you believe that the practice of "evergreening"—by which brand-name pharmaceutical companies obtain follow-on patents for often superficial or peripheral applications, such as a pill coating, to forestall generic competition—places a burden on the patient and societal benefits of innovative research?

Answer. The mission of the NIH is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. Much of the research supported by the NIH is basic in nature, and the findings are published to inform the broader research community. The commercial sector may also use this information to inform their product discovery efforts. An analysis of 210 FDA approved drugs (2000–2016) and the published research associated with these drugs suggests that nearly 90 percent of the public sector funding underlying first-in-class drugs supported basic research of biological mechanisms, rather than drug-specific research (Cleary et al., PNAS, March 6, 2018). Every drug, whether first-in-class or a competing follow-on, was associated directly or indirectly with NIH-funded research. When the patent and regulatory exclusivity periods for these drugs end, they become generic.

The NIH licenses technologies arising from the NIH intramural research program. Only 35 (11 percent) of the 328 license agreements executed by the NIH in fiscal year 2017 were exclusive licenses. In 2018, NIH executed 329 license agreements, of which 26 (8 percent) were exclusive. The category of exclusive licenses often includes more than one exclusive license for a patented technology based on separate fields of use, e.g. a potential cancer therapy where one company develops it for blood cancers, another for solid tumors, and a third only in combination with its existing brand name drug. The category of non-exclusive license agreements includes commercial use of patented technologies and licenses for non-patented research materials such as cell lines, animal models and antibodies, which companies use in their

research and development programs. NIH does not charge fees to transfer these non-patented research materials to non-profit researchers.

Thus, NIH funding supports much basic research that is ultimately used by many for-profit researchers to develop new drugs for the prevention and treatment of disease conditions. Non-profit researchers make use of these published findings to further the understanding of biological processes and sometimes the development of new drugs. The innovative output of the US biomedical sector depends on this foundational government support. NIH manages the licensing of its own inventions in a manner that balances public health needs with incentives required by the private sector to bring new products to market. The NIH has no comment on the patent system because it is beyond the purview of NIH.

COST OF SPECIALTY ONCOLOGY DRUGS

Question. The cost of specialty oncology drugs has increased more than 500 percent from 2006 to 2015, which is only expected to continue. Several studies and clinical trials, including those supported by NCI, have demonstrated significant cost savings from examination of de-escalation in dose, schedule, or duration of oncology medications, or simply by taking medication with or without food. Such trials can be self-financing, in that the relative savings from the optimized doses could be put toward the trial operation. For example, the NCI recently supported an international randomized study comparing a 75 percent dose reduction (with food) to standard dosing for the prostate cancer drug, abiraterone, which demonstrated no decline in efficacy with the lower dose. Separately, the National Eye Institute funded a study in 2011 to examine optimal dosing for ranibizumab.

Does NIH believe that there may be a potential clinical benefit for patients to the study of optimal drug dosing and frequency regimens, in particular for oncology medications?

Answer. The NCI conducts and supports research to identify when patients will benefit from treatment, and when multiple therapies will not provide patient outcomes. Reducing the frequency and number of therapies a patient receives during cancer treatment not only reduces healthcare costs but often minimizes the risk of side effects, complications, and long-term (late) effects. Researchers are capitalizing on advances in molecular and genetic profiling of cancers to develop clinical studies that will help to identify when it is appropriate to de-escalate doses, adjust treatment schedules, or shorten the duration of oncology therapies.

The mission of the NCI clinical trials programs includes an emphasis on filling gaps in the national cancer research effort and avoiding duplicating on-going private sector efforts. Research questions focused on de-escalation of standard therapies, or distributing less therapy, are not likely to be answered by industry-sponsored trials—leaving a research gap that the NCI's clinical trials program seeks to fill. Removing or de-escalating well-accepted standard therapies in oncology requires significant care. Randomized trials are the gold standard, but require large numbers of patients and rigorous study design. NCI has supported several de-escalation studies through its National Clinical Trials Network, including recent trials in breast cancer and head and neck cancer.

The Trial Assigning Individualized Options for Treatment (TAILORx) was a large phase 3 trial designed to evaluate the benefit of chemotherapy for patients with certain early stage breast cancers and an intermediate risk of recurrence based on the 21-gene breast cancer assay, Oncotype DX. Between 2006 and 2010, more than 10,000 patients were screened and more than 6,700 with a moderate risk of recurrence were randomized between hormonal therapy alone vs. hormonal therapy plus chemotherapy. The trial was designed to show that hormonal therapy alone is as effective at preventing recurrence, second cancers, or death as hormonal therapy plus chemotherapy. The trial results, published in the New England Journal of Medicine in July 2018, demonstrated that hormonal therapy alone and hormonal therapy with chemotherapy were similarly effective in this patient population, although some benefit of chemotherapy was found in some women over 50 years old.[126] This de-escalation trial demonstrated that chemotherapy could be safely dropped from therapy for this early stage breast cancer patient population—saving thousands of patients the burden and toxicity associated with chemotherapy treatment.

Human papillomavirus (HPV)-driven head and neck (oropharyngeal) cancers have significantly better survival rates than tobacco and alcohol-induced head and neck cancers. HPV-positive (HPV+) patients are typically younger, healthier, and often likely to survive their disease. The goal of de-escalation trials for patients with HPV+ oropharyngeal cancers is to see if short and long-term toxicity can be re-

[126] https://www.ncbi.nlm.nih.gov/pubmed/29860917.

duced while maintaining high survival rates. The Phase 3 NRG/RTOG–1016 trial was designed to see if the medication cetuximab therapy plus radiotherapy (RT) was as effective at controlling HPV+ oropharyngeal cancers as standard cisplatin therapy with RT, but with fewer side effects. The study opened in 2011 and closed in 2014, having screened 987 patients for HPV+ tumors and randomizing 849 patients between the two therapeutic approaches. However, the trial's results, which were published in Lancet in January 2019, confirmed that cisplatin and radiation should remain the standard of care for HPV-related oropharyngeal cancers.[127] This trial demonstrated the importance of testing such hypotheses to ensure that patients continue to receive the best care for their disease.

In addition to de-escalating, investigators also seek to identify the optimal dosing schedule for cancer therapies. For example, a recent collaboration between NCI intramural investigators in the Center for Cancer Research (CCR) and the University of Chicago Comprehensive Cancer Center seeks to identify when the interval between cancer therapy doses can be safely increased. This research uses pharmacological modeling, which predicts the effect of different doses and timing based on knowledge of disease processes and the rate at which drugs are cleared from the body. Initial results suggest that, following the initial treatments, the interval between later doses of two cancer therapeutics can be increased without sacrificing efficacy in most patients. The treatment schedule identified by this work would result in a potential 70 percent cost savings for treatment with the medications Pembrolizumab, which is used to treat a number of cancers including melanoma and non-small cell lung cancer, and Nivolumab, which is approved for treatment of non-small cell lung cancer.[128] Advances in precision medicine, or choosing a therapy based on a cancer's particular genetic and molecular profile, may also ultimately help to contain healthcare costs. Recent work by several researchers in NCI's CCR have focused on classifying several types of cancer, including melanoma,[129] diffuse B-cell lymphoma,[130] and liver cancer[131] into discrete subtypes based on gene expression patterns, as well as identifying molecular similarities between different tumor types. Identifying these different subtypes allows researchers and clinicians to better predict which treatments are likely to be effective for a patient and limit the use of expensive therapies with little hope of activity and potentially drive down costs.

As NCI leaders discussed in a recent article feature in the Journal of the American Medical Association (JAMA), the costs of conducting the clinical trials required for drug approvals contribute to the list prices of pharmaceutical products. The average per-patient costs have increased dramatically during the past two decades, an important factor in the total costs of drug discovery and development. Therefore, NCI is working to ensure that trials are appropriately sized to answer the scientific questions they pose, developing trials with fewer patients whenever possible. For example, in some trials of highly active agents, it may be possible to evaluate the drug without traditional control trials arms, instead relying on "synthetic" control groups created from data from previous trials. NCI is also considering the use of novel end points for clinical trials that are based on the agent's mechanisms of action and conducted through the aggregation of new and existing data.[132]

NCI will continue to work closely with the FDA and other Federal agencies and support research on the best therapeutic approaches for patients.

CHILDHOOD TRAUMA

Question. So many children nationwide grow up in homes where they witness violence or drug misuse, or face abuse or neglect. I see this all over Chicago, but also in rural communities in my state. With the Adverse Childhood Experiences (ACEs) study, we now understand how this toxic stress from these situations can have serious, long-term impacts on the developing mind. Studies show that exposure to multiple ACEs or traumatic experiences increases the likelihood of chronic disease development, mental illness, drug use, poverty, and violence. Thankfully, there are interventions that can help children cope with this trauma, and process the experiences they have faced. This Subcommittee has included my language with Senator Capito each of the past 2 years to prioritize these trauma-informed best practices

[127] https://www.ncbi.nlm.nih.gov/pubmed/30449625.

[128] American Society for Clinical Oncology 2019 Annual Meeting, Poster #107, Abstract #3115: A modeling and simulation study of less frequent dosing of nivolumab 480 mg. Peer, Cody J.; Goldstein, Daniel A.; Figg, William D.; Ratain, Mark J.

[129] https://ccr.cancer.gov/news/milestones-2019/article/predicting-immunotherapy-responses.

[130] https://ccr.cancer.gov/news/milestones-2019/article/sorting-lymphoma-subtypes.

[131] https://ccr.cancer.gov/news/milestones-2018/article/different-and-the-same.

[132] https://jamanetwork.com/journals/jama/fullarticle/2723062.

in more Federal grant programs. And Section 7132 of the SUPPORT for Patients and Communities Act established a Federal interagency task force to identify and disseminate such trauma-informed best practices. Dr. Collins, what research is NIH doing to study childhood trauma and its impact on long-term mental health and other outcomes, as well as interventions to mitigate the impact of such adversity? What more do we need to study?

Answer. NIH, acting largely through NICHD, and NIMH, supports research on the mental and physical health effects of trauma, including funding investigator-initiated research related to improving our understanding of childhood trauma and its long-term impact and broadening the evidence-base needed to improve treatments, interventions, and mental health services for trauma survivors.

The NICHD Pediatric Trauma and Critical Illness Branch was established in 2012 to coalesce the science in trauma, injury and critical illness across the Institute and to grow the field in these areas across the continuum of care.[133] Of particular interest are studies that examine interactions between physical and psychological trauma, emergency medical services to children, injury prevention and the provision of critical care medicine to the most vulnerable children.[134] The Branch's research portfolio on psychological trauma, traumatic stress, violence, and child maltreatment supports projects that examine the psychological processes that co-occur with physical trauma, which affect treatment, recovery, and well-being. To grow and maintain the pipeline of research experts in this area, NICHD also supports research training programs, such Career Development Awards, focused on training in child maltreatment research, and a national physician scientist training program for pediatric trauma surgeons and intensive care physicians.[135]

Recently, NICHD called for research resource-related projects on the epidemiology and prevention of injury, receiving an excellent response from the field. Among the projects funded is a study on the value of pediatric readiness in the emergency care of injured children. Its major goal is to construct a large, multi-State dataset to determine if pediatric readiness in emergency medicine will result in improved quality of care, patient health outcomes, and costs of care for injured children. This project will produce the largest population-based, pediatric trauma database, a unique research resource that would fill important knowledge gaps in pediatric trauma care and help to identify a re-engineered, high-value emergency care system for injured children that optimizes quality, outcomes, and costs. A second project was funded to provide a research and treatment resource for the management of psychological distress in children who have been hospitalized for a physical trauma. The researchers are developing multi-media therapeutic modules to ameliorate post-traumatic stress symptoms and associated psychological impairment in children after an injury to improve health related quality of life.

NICHD's hallmark program is the Capstone Centers for Child Maltreatment Research and Training. In 2018, funding was awarded to three new centers (for a total of four) to serve as national resources for research on the prevention, screening and treatment of child abuse and neglect.[136] This program has already been productive; findings recently released from the first center showed that adverse childhood experiences, including being abused and having parents with mental health issues, are associated with higher out-of-pocket healthcare costs later in life.

NIMH recognizes that psychological trauma is an emotionally painful, shocking, stressful, and sometimes life-threatening experience. The cumulative nature of adverse childhood experiences can increase the risk for poor mental and physical health outcomes.[137] To better understand trauma-related risk trajectories and how early life adversity shapes emotional, cognitive, and brain development, NIMH is supporting a landmark study on the developmental precursors of mental illnesses.[138] Researchers are following mothers and their infants over the first 3 years of life to characterize development across multiple levels of analysis, from environmental risk to physiology to neural circuits to behavior. This research has the potential to define the contributions of modifiable factors (psychosocial adversity, inflammation, and early caregiver support) to the earliest indicators of risk for psychopathology, and may pave the way for innovative early interventions, and a greater understanding of childhood trauma.

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[133] https://www.nichd.nih.gov/sites/default/files/publications/pubs/Documents/Pediatric Trauma__Action__Agenda.pdf.

[134] https://injuryprevention.bmj.com/content/injuryprev/21/6/441.full.pdf.

[135] https://www.nichd.nih.gov/research/supported/pcctsdp.

[136] https://www.nichd.nih.gov/newsroom/news/100418-child-maltreatment-research.

[137] https://www.ncbi.nlm.nih.gov/pubmed/16311898.

[138] https://projectreporter.nih.gov/project__info__description.cfm?aid=9518320.

There remain many unanswered questions in the field of childhood trauma. Currently, NIMH supports over 120 human and animal research projects related to post-traumatic stress disorder (PTSD) across the lifespan. Through a robust traumatic stress research program that includes basic, translational, and services and intervention research,[139] NIMH seeks to gain a deeper understanding of how exposure to traumatic stress affects individuals, and how to improve ways of identifying those at risk before adverse reactions develop. Current NIMH priorities also include testing preventive interventions to preempt PTSD, developing new treatments for PTSD, and making existing PTSD treatments more effective and accessible.

QUESTIONS SUBMITTED BY SENATOR JACK REED

CHILDHOOD CANCER

Question. As you know, there is strong bipartisan support for the Childhood Cancer STAR Act, which was signed into law last year. For fiscal year 2019, we provided $30 million to fund this law, the largest piece of which we anticipated would be dedicated to developing a national childhood cancer biorepository. What progress have you made in this area, and how much of the $30 million provided by Congress do you anticipate investing in the biorepositories this year?

Answer. NCI appreciates the strong bipartisan support for childhood cancer research demonstrated through passage of the Childhood Cancer STAR Act, and NIH is committed to implementing its provisions. At NCI, efforts are underway to implement the childhood cancer survivorship research and biospecimen and biorepository research provisions, as well as other provisions focused on enhancing pediatric expertise on NCI advisory boards, and continued reporting on childhood cancer research activities.

NCI continues to make progress in expanding and enhancing biospecimen collection and related research. For many years, NCI has supported the Children's Oncology Group (COG) and the COG Biorepository, and these efforts serve as NCI's central effort to bank biospecimens from children and adolescents with cancer for future research use. The Institute is hosting a scientific meeting in May 2019 to bring together representatives from across the COG, including those involved in the COG Biorepository, and subject matter experts from across the childhood cancer research community who focus on specimen collection for cancer subtypes that are most refractory to treatment. NCI has invited colleagues from the Centers for Disease Control and Prevention's National Program of Cancer Registries to this meeting, as well as members of the childhood cancer advocacy community.

This meeting will provide an opportunity to discuss specimen collection and biobanking challenges, particularly those related to specimen sharing across institutions, standardization of specimen annotation, and specimen quality control. The meeting will also focus on opportunities to further enhance specimen collection and storage, to encourage greater collaboration across institutions, to collect additional high-priority specimens outside the context of clinical trials, and to ensure that any new specimen collection efforts are complementary to those underway, such as ongoing collection and analysis of specimens at relapse through the NCI–COG Pediatric MATCH trial.[140]

We look forward to the valuable guidance and input this discussion will provide to the entire childhood cancer research community, which may inform any additional new biospecimen collection efforts or biorepository resource enhancements in fiscal year 2019, fiscal year 2020, and beyond, to further implement these provisions of the STAR Act. While NCI is committed to making significant investments to advance this important work, we also recognize that the STAR Act authorization of $30 million per year covers all sections of the legislation, including aspects of the law that are directed at other entities within the Department of Health and Human Services.

In fiscal year 2019, NCI is making several new investments to support biospecimen collection and analysis that align with STAR Act provisions. These include biospecimen analysis studies within NCI pediatric and the adolescent and young adult (AYA) clinical trials;[141] the NCI Pediatric Oncology Branch MyPART (My Pediatric and Adult Rare Tumor) Network;[142] and the Center for Pediatric Tumor Cell Atlas,

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[139] https://www.nimh.nih.gov/about/organization/dtr/traumatic-stress-research-and-dimensional-measurement-and-intervention-program/index.shtml.

[140] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match.

[141] https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp.

[142] https://www.cancer.gov/nci/pediatric-adult-rare-tumor.

part of the Cancer Moonshot Human Tumor Atlas Network. The Center, located at the Children's Hospital of Philadelphia, will focus on three high-risk cancer subtypes that combined, account for 50 percent of all pediatric cancer deaths: high-grade glioma, high-risk neuroblastoma, and very high risk acute lymphoblastic B-cell precursor leukemia.[143] NCI has also prioritized additional new funds in fiscal year 2019 for our National Clinical Trials Network Groups, including COG, to improve patient enrollment in clinical trials. Efforts are also underway through the Cancer Moonshot to perform retrospective analysis on pediatric biospecimens. The retrospective analysis involves additional sequencing of specimens from several completed COG trials, allowing for in-depth annotation of these specimens to support future research. These investments are all in addition to NCI's long-term commitment to supporting specimen collection through COG clinical trials, and specimen storage through the COG Biorepository.

There is a compelling need for the childhood cancer research and advocacy community to discuss opportunities specific to biospecimen collection and biorepository resources. Understanding these insights is best before we develop any new funding opportunity announcements to ensure that these rare and much needed research participant contributions are maximally impactful. With that principle in mind, NCI anticipates that fiscal year 2020 STAR Act implementation activities will expand emphasis on biorepositories, whereas fiscal year 2019 STAR Act implementation activities will include greater emphasis on survivorship research.

Question. Can you provide additional details on the President's childhood cancer initiative and how it will coordinate with the STAR Act programs? Can you confirm that this $50 million request is in addition to the $30 million in funding that we secured in fiscal year 2019 (and which we are seeking on a bipartisan basis to build on in fiscal year 2020)?

Answer. There are approximately 16,000 children and adolescents diagnosed with cancer in the United States each year. The President's Budget proposes an additional $50 million in fiscal year 2020, to continue for 10 years and provide a total of $500 million to support the Childhood Cancer Data Initiative. This initiative focuses on the critical need to obtain and analyzing data to learn from children with cancer. This information, spanning the spectrum of tumor analysis to clinical care and outcomes of each child, will underpin our ability to develop new approaches to cure children with cancer.

The additional resources of $50 million in fiscal year 2020 will allow the NCI to expand efforts to collect data, to make strides in federating existing sources of data, to ensure that data concerning childhood cancers are appropriately accessible and used, and to incentivize the cancer research community to develop new treatments for children with cancer. The initiative is a promising opportunity to enhance our ability to improve outcomes for children with cancer—first by learning from every one of these children in an intentional and organized manner and second by developing more efficient ways to share and use the information. We envision that it will aggregate the necessary information to foster essential research while also increasing available information about each child's illness. Such information will include extensive sequencing of tumors and additional clinical information regarding each child's response to treatment.

NCI is hopeful that the Childhood Cancer Data Initiative will also serve as a force multiplier for efforts aligned with implementation of the Childhood Cancer STAR Act. NCI-supported biospecimen collection and associated data would all contribute to the aggregated data resources NCI plans to develop through the initiative. NCI would also aim to integrate data collected though new and continued childhood cancer survivorship research projects and ongoing longitudinal studies (e.g., Childhood Cancer Survivor Study, St. Jude Lifetime Study) through the initiative. New data linkages and resources may also enable the cancer research community to establish additional cohorts to complement the Childhood Cancer Survivor Study, allowing NCI to study the long-term effects of new immunotherapy and targeted chemotherapy treatments. NCI is also exploring opportunities to leverage data collected through NCI and CDC cancer registries programs, including data collected though CDC's early case capture efforts for pediatric and young adult cancer cases. This program is a central piece of CDC's STAR Act implementation, and the Childhood Cancer Data Initiative has the potential to further build upon that work.

In summary, NCI will continue these important research efforts with whatever resources are available to us. If appropriated, the President's Budget request envisions the $50 million proposed for the Childhood Cancer Data Initiative as additional new resources. In the current fiscal year, NCI is supporting implementation of the STAR Act provisions that are directed toward the Institute. For example, in

[143] https://projectreporter.nih.gov/project__info__description.cfm?aid=9627531&icde=0.

addition to continuing to conduct and support childhood, AYA cancer survivorship research, NCI is expanding support in this area for new research projects. Specifically, NCI issued a new request for applications in fiscal year 2019. We estimate that we will allocate approximately $4.8 million per year for 5 years, to this survivorship research priority, subject to receiving meritorious applications and future fiscal year funding, among other considerations. NCI is also working to enhance biospecimen collection, biobanking, and related resources for childhood and AYA cancers, with an emphasis on those cancer types and subtypes for which treatments are least effective, as specifically encouraged in the STAR Act.

SUICIDE

Question. CDC reported in June 2018 that the suicide rate has risen 30 percent since 1999. Given this national crisis, can you discuss what research is being conducted on suicide prevention research at the NIMH and how does NIMH set research priorities specific to suicide and suicide prevention?

Answer. Suicide prevention research continues to be a top priority for NIH.[144] Over the past several years, NIH has steadily increased its support for suicide research. NIH spent approximately $46 million on suicide research in fiscal year 2015, $52 million in fiscal year 2016, $68 million in fiscal year 2017, and $96 million in fiscal year 2018.

As the lead Federal agency for research on mental disorders, the National Institute of Mental Health (NIMH) within the NIH takes a central role in research aimed at identifying at-risk individuals and developing new treatments and interventions, ultimately to improve quality of life and prevent death. NIMH recognizes that comprehensive suicide prevention efforts require multiple approaches, with the following research projects exemplifying some of our most promising tools.

Identifying At-Risk Individuals:

—*Implementing Universal Screening:* The Emergency Department Safety Assessment and Follow-up Evaluation (ED–SAFE) study demonstrated that a three-item screening tool improved providers' ability to identify adults at risk for suicide.[145] This study showed that when screening was conducted for all patients—regardless of the reason for their emergency department (ED) visit—suicide risk detection increased nearly twofold. If these findings remain true when scaled up, the public health impact could be tremendous, because identification of risk is the first and necessary step for preventing suicide.

—*Maximizing Electronic Health Records:* Building on the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS),[146] the largest study of mental health risk and resilience ever conducted among military personnel, researchers from NIMH partnered with the Department of Veterans Affairs (VA) and other collaborators to develop predictive models of suicide risk among veterans receiving VA healthcare. This research demonstrated the feasibility of developing algorithms to identify patients within the VA system whose predicted suicide risk was 20–30 times higher than average. Suicide prevention coordinators at each VA facility work with these patients and their clinicians on suicide-focused clinical assessment and ways to enhance treatment. Other healthcare systems are beginning to use data from electronic health records in novel ways to help identify people with suicide risk, including many of the 13 healthcare systems across the United States that are part of NIMH's Mental Health Research Network.[147]

Developing New Treatments and Interventions:

—*Strengthening Mental Health Support:* NIMH continues to support research to identify effective interventions for individuals at risk for suicide. One such intervention is Safety Planning Intervention (SPI), in which a clinician collaborates with the patient to identify specific strategies to decrease the risk of suicidal behavior, such as ways to reduce the patients' access to lethal means during a time of crisis, and to identify personalized coping strategies. NIMH is supporting an evaluation of the implementation of the Zero Suicide approach, including SPI, in 145 community mental health clinics across New York.[148] In addition, NIMH's ED–SAFE study, which focused on ED patients at risk for suicide, found that brief interventions in the ED, plus follow-up phone calls to the

[144] https://www.nimh.nih.gov/about/director/messages/suicide-prevention.shtml.
[145] https://www.ncbi.nlm.nih.gov/pubmed/26654691.
[146] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4286426/.
[147] https://www.ncbi.nlm.nih.gov/pubmed/29792051.
[148] https://projectreporter.nih.gov/project__info__description.cfm?aid=9514242.

patient by a clinician, reduced suicide attempts by about 30 percent during a 12-month period.[149]

—*Deploying Fast-Acting Pharmacologic Interventions:* NIMH research has also supported the study of fast-acting treatments for individuals with acute suicide risk. Ketamine, an anesthetic that has been around for decades, is emerging as a rapid onset intervention. NIMH researchers showed that suicidal ideation (in the context of major depressive disorder) was reduced within 40 minutes of a ketamine infusion and remained improved for up to four hours post-infusion.[150] A subsequent meta-analysis reported that a single infusion of ketamine reduces suicidal ideation for up to one week.[151] In March 2019, the FDA approved Spravato™, an esketamine nasal spray (a form of ketamine), in conjunction with an oral antidepressant, for treatment-resistant depression.[152] This treatment is only available at a trained doctor's office or clinic to mitigate potential risks. The makers of Spravato™ are also conducting clinical trials of intranasal esketamine in participants at imminent risk for suicide.[153]

NIMH's overall research priorities continue to be informed by strategic planning and include the input of stakeholders, advisory committees, and NIMH leadership. In developing these priorities, NIMH strives to balance public health needs and scientific opportunities, taking into consideration portfolio balance among other factors. For example, specific to suicide prevention, the stakeholder-informed Prioritized Research Agenda for Suicide Prevention is an available resource that can be used to help identify gaps in the NIMH suicide prevention portfolio.[154] NIMH only funds research which is judged highly meritorious and follows a two-stage peer review process.

Question. The recently released action plan from the National Action Alliance for Suicide Prevention outlines the need to develop a prioritized approach for allocating funds and monitoring future suicide research to ensure that available resources are directed towards research with the greatest likelihood of reducing suicide deaths. Has NIH reviewed these recommendations and, if so, what does NIH plan to do with the recommendations?

Answer. NIMH is working with scientists and stakeholders to address the increasing incidence of suicide across the country, focusing on identifying research gaps, challenges, and opportunities to inform how to make change now and in the longer-term. Under the leadership of former NIMH Director Thomas Insel, M.D., the Research Prioritization Task Force (RPTF) aimed to advance the efforts of the National Action Alliance for Suicide Prevention (NAASP), a public-private partnership among Federal agencies, State governments, private companies, and national suicide prevention advisory and advocacy groups. As part of the RPTF, NIMH helped to develop the Prioritized Research Agenda for Suicide Prevention.[155] The Agenda identifies research gaps, such as limitations in understanding of the etiology and course of suicidal ideation and behavior, the need for new interventions specifically targeting suicide, better matching of existing treatments to individual needs, and implementation of effective suicide prevention practices.

NIMH has initiated research opportunities to address research gaps identified in the Agenda, such as studies to develop and test screening approaches for use in EDs to identify youth at risk for suicide, and develop methods to help assign youth who screen positive to appropriate interventions.[156] NIMH also partnered with other NIH Institutes and Centers to support projects leveraging existing data sets to improve our understanding of risk trajectories and subgroups at risk for suicide, while addressing suicide research gaps in mortality outcomes.[157,158] To further address gaps in the research workforce, NIMH issued a notice of special interest to expand the number of mental health researchers—both established scientists, as well as early career scientists—who engage in suicide research.[159]

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[149] https://www.ncbi.nlm.nih.gov/pubmed/28456130.
[150] https://www.ncbi.nlm.nih.gov/pubmed/20673547.
[151] https://www.ncbi.nlm.nih.gov/pubmed/28969441.
[152] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632761.htm.
[153] https://www.ncbi.nlm.nih.gov/pubmed/29656663.
[154] https://theactionalliance.org/resource/prioritized-research-agenda-suicide-prevention-action-plan-save-lives.
[155] https://theactionalliance.org/resource/prioritized-research-agenda-suicide-prevention-action-plan-save-lives.
[156] https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-070.html.
[157] https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-18-400.html.
[158] https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-18-410.html.
[159] https://grants.nih.gov/grants/guide/notice-files/NOT-MH-19-026.html.

In addition, NIMH partners with NAASP to support their Zero Suicide initiative.[160] Zero Suicide is a commitment, a goal, and a campaign to prevent suicide attempts and deaths among individuals receiving treatment within healthcare systems. NIMH is funding several projects aimed at Zero Suicide to create a stronger basis for dissemination and large-scale implementation of effective risk detection, intervention, and service delivery strategies for suicide prevention in real world settings.[161] This effort is also consistent with the NIMH Strategic Plan for Research, Objective 4, improving public health through more practice-ready suicide prevention interventions.[162]

QUESTIONS SUBMITTED BY SENATOR PATRICK J. LEAHY

MIGRAINES

Question. Migraine is currently the second leading cause of all global disability. Unfortunately, due in part to limited research and treatment, inappropriate opioid prescriptions for migraine present Americans with ongoing risks of opioid use disorders and have worsened outcomes in patients. The NIH website on disease burden shows "migraine" to have received by far the lowest level of research funding in 2015, among those diseases with the highest burden. In 2017, only 53 extramural investigators were funded for headache research, compared to 315 for epilepsy and 385 for schizophrenia, each of which has far lower burden than migraine. While migraine grant proposals are eligible for consideration under the HEAL RFAs recently issued for pain research, I am very concerned that these will fail to attract enough investigators to this historically under-funded research area.

Does NIH have plans to issue specific RFA programs for headache disorders research, comparable in scope to the BACPAC group of RFAs for research on back pain?

Answer. NIH recognizes the burden of headache disorders as prevalent and disabling conditions for patients around the country.

NIH has identified priority areas of need unique to headache research, including fundamental mechanisms to guide new treatment development and advancing treatments through the clinical pipeline. Importantly, headache research is an area with trans-NIH interest for which funding has increased from $18 million in 2010 to $32 million in 2018. NIH has supported important research that is providing exciting new therapies for headache. Basic research on potassium channels, delta or kappa opioid receptors, and TRP channels has fundamentally increased our understanding of trigeminal nociceptors and their involvement in initiating a migraine, giving us new targets for potential treatments. NIH investigators also provided the foundation for development of calcitonin gene receptor protein (CGRP) antibodies now used for migraine therapy. In addition, NIH sponsored research also led to efforts exploring the promising avenue of vagus nerve stimulation for headaches. Lastly, a pivotal trial on pediatric migraine is shifting clinical practice toward safer and more effective therapies. These exciting advances are all examples of NIH efforts toward relieving the burden of headache disorders.

In addition, NIH's long-standing programs in these specific areas will be greatly enhanced by the recently launched HEAL (Helping to End Addiction Long-term) initiative and its efforts to advance the research agenda for pain and care across pain conditions. Through HEAL, NIH released many funding opportunity announcements for research on biomarker discovery, device and drug development, clinical trials on effectiveness of interventions and pragmatic trials for implementation of effective therapies for pain conditions. Headache research fits within the scope of all these initiatives and NIH has made strong efforts to network with and encourage the headache research community to submit applications to these solicitations. Furthermore, the infrastructure and resources being established through the HEAL initiative will be available to enhance pain research across all conditions which will greatly inform new areas of mechanisms for headache research.

The HEAL BacPac Initiative was designed to fill a unique need for another highly prevalent pain condition for which much of the research framework is inadequate. Back pain is unique in that it lacks accurate diagnostic tools and assessments, a clear classification scheme based on causality, understating of the underlying mechanisms, and effective treatment approaches. Unlike the case for back pain, the diagnostics and classifications for headache disorders are better established and our

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[160] http://zerosuicide.sprc.org/.
[161] https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-16-800.html.
[162] https://www.nimh.nih.gov/about/strategic-planning-reports/strategic-objective-4.shtml.

understanding of the mechanisms of headaches is moving forward through existing programs and can be further advanced through HEAL with the participation of the headache research community.

CARDIOVASCULAR DISEASE

Question. Over the past half-century, we have witnessed unprecedented progress in addressing cardiovascular disease, yet recent trends show that declines in heart disease and stroke mortality rates have slowed for all races and are increasing substantially among certain population groups such as rural, middle-aged white Americans. The American Heart Association recently announced new alarming data that shows that nearly half (48 percent) of U.S. adults have some form of cardiovascular disease.

As our Nation's population ages, there is an urgent need for action to improve innovation in the treatment of cardiovascular disease. What is NIH doing to address the high rates of cardiovascular mortality, especially in rural areas like my home State of Vermont?

Answer. The NIH is committed to ensuring that all Americans benefit from the life-saving advances made possible by federally funded research—regardless of their race, age, sex, income, or where they live. The National Heart, Lung, and Blood Institute (NHLBI) leads NIH's support for research on cardiovascular disease (CVD). Over the past 50 years, research funded by the NHLBI has helped bring about a 71 percent decline in deaths from CVD nationwide. However, CVD remains the Nation's leading cause of death, with the highest mortality concentrated in certain groups, including African Americans, American Indian/Alaska Natives, and rural communities. We are supporting research to determine what causes these health disparities and how to correct them.

High blood pressure is a leading risk factor for heart disease and stroke. Given that blood pressure medication dosing and adherence is a major challenge in rural and underserved communities, NHLBI is supporting innovative methods to help patients connect with pharmacists. For example, NHLBI's Collaboration Among Pharmacist and Physicians toto Improve Outcomes Now (CAPTION) study embedded pharmacists within 32 primary care physicians' offices in 15 states, serving high-risk socioeconomic and racial groups. After 9 months, patients treated through this physician-pharmacist team approach had sustained reductions in blood pressure, compared to patients who received usual care.[163] Another recent NHLBI-funded study found that having blood pressure screenings and pharmacist consultations in barbershops helped men lower their blood pressure.[164] Innovative programs like these could be adapted and used in rural settings to reduce hypertension and other cardiovascular risk factors.

A new NHLBI program launched in March 2019, Disparities Elimination through Coordinated Interventions to Prevent and Control Heart and Lung Disease Risk (DECIPHeR) will help bring evidence-based interventions like these to communities with a high burden of CVD. DECIPHeR researchers will form partnerships with local healthcare systems, government agencies, and community organizations so researchers and community members can work together to design, test, and sustain effective approaches to deliver proven treatments.[165]

NHLBI also recently solicited proposals for new large cohort studies to address research on heart, lung, blood, and sleep disorders, with an emphasis on groups that are currently not well represented, including rural communities.[166] We expect to fund three such cohorts later this year.

NHLBI also supports research to address CVD through telehealth. This could include the use of audiovisual technology to deliver remote care for patients who live in remote areas or have other challenges accessing primary healthcare centers. For example, an ongoing NHLBI-funded study is evaluating the effectiveness of traditional center-based cardiac rehabilitation combined with telemedicine-guided rehabilitation at home.[167] NHLBI is also funding a study to collect national data on the use of telemedicine in intensive care units to identify best practices.[168]

Rural patients have traditionally been underrepresented in cardiovascular clinical trials, yet have a higher burden of CVD than patients from metropolitan areas. We are working to increase enrollment of rural patients in NHLBI's Cardiothoracic Surgical Trials Network, which has made significant contributions in advancing the evi-

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[163] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063695.
[164] https://www.ncbi.nlm.nih.gov/pubmed/29527973.
[165] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-20-003.html.
[166] https://grants.nih.gov/grants/guide/pa-files/PAR-18-577.html.
[167] https://projectreporter.nih.gov/project__info__description.cfm?aid=9588024.
[168] https://projectreporter.nih.gov/project__info__description.cfm?aid=9061809.

dence base for cardiothoracic surgery. Dartmouth-Hitchcock Medical Center in New Hampshire and Maine Medical Center were recently linked to the network to expand its reach into rural communities of Northern New England.[169]

NIH PAIN CONSORTIUM

Question. Pain is a significant public health issue affecting an estimated 69.6 million Americans each year. According to the Institute of Medicine, the total incremental cost of healthcare due to pain management in the U.S. is estimated to range from $560 billion to $635 billion, amounting to approximately 2.8 to 3.5 percent of our Nation's total GDP. This cost estimate combines the direct medical costs of pain management care as well as the economic costs related to lost productivity and disability programs. With little known about alternatives for treating and managing relief from pain, medical providers are often limited to prescribing highly addictive opioids or muscle relaxants to help patients mitigate symptoms from pain.

Unfortunately, addiction to opioid painkillers has ravaged the Nation, and the number of opioid prescriptions has tripled in the past 20 years alone. In 1996, the National Institutes of Health (NIH) established the NIH Pain Consortium to develop a strategy for research on pain. Since then, the NIH has worked to expand research in this area, while incorporating the work and expertise of stakeholders to find ways to better serve patients.

Has the NIH Pain Consortium approached research on exploring opioid alternatives to treating and managing both acute and chronic pain? If so, please describe past, present, and ongoing projects in this area. If not, please describe if the NIH plans to develop more research focused on finding opioid alternatives to treating and managing acute and chronic pain.

Answer. The NIH recognizes the significant public health crisis and individual burden of pain and supports research to better understand, manage and treat acute and chronic pain to relieve the burden of pain and reduce our reliance on prescription opioid medications.

The NIH Pain Consortium is a collaboration of 27 Institutes, Centers, and Offices (ICOs) across the NIH charged with promoting and coordinating pain research across the agency. In 2018 the NIH Pain Consortium ICOs collectively spent $605 million on a wide range of research collectively aimed at understanding the mechanisms of pain, new targets for treatment, and more. NIH has existing programs to support development of novel and non-addictive treatments for acute and chronic pain, from early-stage drug target discovery of 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. Through these programs, NIH researchers identified nerve growth factor receptor and pain-related ion channel 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, NIH currently is funding research to develop a non-addictive treatment for headache and non-opioid analgesics for diabetic nerve pain.[170]

The NIH Pain Consortium worked with the Interagency Pain Research Coordinating Committee to develop the Federal Pain Research Strategy [171] (FPRS), which outlines a long-term strategic plan to guide NIH and other Federal agencies in making their funding decisions to advance pain research. The development of safer opioids and new, non-opioid analgesics were considered high priority research areas in this strategy.

The NIH Pain Consortium, with the FPRS as a guide, has been involved in developing and implementing the recently released NIH HEAL (Helping to End Addiction Long-term) Initiative,[172] which aims to 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

[169] https://projectreporter.nih.gov/project__info__description.cfm?aid=9755050.

[170] https://projectreporter.nih.gov/project__info__description.cfm?aid=9325694&icde=36528658&ddparam=&ddvalue=&ddsub=&cr=3&csb=default&cs=ASC&pball=.

[171] Federal Pain Research Strategy: https://iprcc.nih.gov/sites/default/files/iprcc/FPRS__Research__Recommendations__Final__508C.pdf.

[172] The NIH HEAL Initiative: https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative.

and accelerate the development of non-addictive treatments, and rapidly advance new treatments to the clinic. Through HEAL, NIH supports biomarker discovery and validation to inform early phase clinical testing of potential non-addictive pain therapies. To improve success in bringing medications to the clinic, HEAL 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, NIH is establishing the HEAL Early Phase Pain Clinical Network to test new, non-addictive pain treatments through clinical trials. The HEAL initiative also is establishing a pain management effectiveness research network to support large clinical trials to test the effectiveness of pharmacological and non-pharmacological treatments across many pain conditions.

NIH is working with Federal partners to provide the infrastructure through the NIH Health Care Systems Research Collaboratory for implementation of non-pharmacological treatments into healthcare systems, with the ultimate goal to embed evidence-based best pain management practices in clinics. These efforts represent unprecedented expansion of the NIH pain research portfolio.

QUESTIONS SUBMITTED TO DOUGLAS LOWY, M.D.

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

CHILDHOOD CANCER

Question. There is strong bipartisan support for childhood cancer here in Congress, as evidenced by the overwhelming support for the Childhood Cancer STAR Act that was signed into law last year. I was very pleased to see the President highlight the vital need to invest more in childhood cancer during his State of the Union and in his Budget Submission to Congress.

How does the President's childhood cancer initiative coordinate with the STAR Act programs? Is your $50 million request for increased childhood cancer funding in addition to the $30 million we are working to provide for the STAR Act?

Answer. There are approximately 16,000 children and adolescents diagnosed with cancer in the United States each year. The President's Budget proposes an additional $50 million in fiscal year 2020, to continue for 10 years and provide a total of $500 million to support the Childhood Cancer Data Initiative. This initiative focuses on the critical need to obtain and analyze data to learn from children with cancer. This information, spanning the spectrum of tumor analysis to clinical care and outcomes of each child, will underpin our ability to develop new approaches to cure children with cancer.

The additional resources of $50 million in fiscal year 2020 will allow the NCI to expand efforts to collect data, to make strides in federating existing sources of data, to ensure that data concerning childhood cancers is appropriately accessible and used, and to incentivize the cancer research community to develop new treatments for children with cancer. The initiative is a promising opportunity to enhance our ability to improve outcomes for children with cancer—first by learning from every one of these children in an intentional and organized manner and second by developing more efficient ways to share and use the information. We envision that it will aggregate the necessary information to foster essential research while also increasing available information about each child's illness. Such information will include extensive sequencing of tumors and additional clinical information regarding each child's response to treatment.

The Childhood Cancer Data Initiative should also serve as a force multiplier for efforts aligned with implementation of the Childhood Cancer STAR Act. NCI-supported biospecimen collection and associated data would all contribute to the aggregated data resources NCI plans to develop through the initiative. NCI would also aim to integrate data collected though new and continued childhood cancer survivorship research projects and ongoing longitudinal studies (e.g., Childhood Cancer Survivor Study, St. Jude Lifetime Study) through the initiative. New data linkages and resources may also enable the cancer research community to establish additional cohorts to complement the Childhood Cancer Survivor Study, allowing NCI to study the long-term effects of new immunotherapy and targeted chemotherapy treatments. NCI is also exploring opportunities to leverage data collected through NCI and CDC cancer registries programs, including data collected though CDC's early case capture efforts for pediatric and young adult cancer cases. This program is a central piece of CDC's STAR Act implementation, and the Childhood Cancer Data Initiative has the potential to further build upon that work.

In summary, NCI will continue these important research efforts with whatever resources are available to us. If appropriated, the President's Budget request envisions the $50 million proposed for the Childhood Cancer Data Initiative as additional new resources. In the current fiscal year, NCI is supporting implementation of the STAR Act provisions that are directed toward the Institute. For example, in addition to continuing to conduct and support childhood, adolescent, and young adult (AYA) cancer survivorship research, NCI is expanding support in this area for new research projects. Specifically, NCI issued a new request for applications in fiscal year 2019. We estimate that we will allocate approximately $4.8 million per year for 5 years, to this survivorship research priority, subject to receiving meritorious applications, among other considerations. NCI is also working to enhance biospecimen collection, biobanking, and related resources for childhood and AYA cancers, with an emphasis on those cancer types and subtypes for which treatments are least effective, as specifically encouraged in the STAR Act.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

ETHYL OXIDE

Question. I'd like to ask about Ethylene Oxide—or EtO—a gas that is widely used for the sterilization of certain medical devices. EtO is a carcinogen. The National Cancer Institute acknowledges that exposure to this gas has been linked to certain types of cancer, including lymphoma, leukemia, and breast cancer. Illinois has three large facilities that currently use EtO, including Sterigenics in Willowbrook, Illinois, which was recently ordered to stop using EtO, after the Environmental Protection Agency measured alarmingly high levels of the gas in neighboring communities. Late last month, the Illinois Department of Public Health issued a report which showed higher rates of certain types of cancers around the Sterigenics facility—including Hodgkins lymphoma and breast cancer in women, and pediatric lymphoma in young girls. While we do not know yet if these cancers are definitively linked to the Sterigenics EtO emissions, they are certainly cause for concern. Dr. Lowy, what do we know about exposure to EtO? What do you make of reports like the one released by the Illinois Department of Public Health?

Answer. The NCI supports a wide range of research to understand associations between exposures and cancer risk, including environmental exposures like ethylene oxide (EtO). NCI is committed to supporting research to increase our understanding of the complexity of cancer risk factors and working with other government agencies responsible for regulating such environmental exposures.

NCI-supported research has contributed to the body of knowledge that has led to the classification of EtO as a carcinogen. EtO is used primarily to produce other chemicals, including antifreeze, and in smaller amounts, EtO is used as a pesticide and a sterilizing agent. The ability of EtO to damage DNA makes it an effective sterilizing agent but also accounts for its cancer-causing activity. Because EtO is highly explosive and reactive, the equipment used for its processing generally consists of tightly closed and highly automated systems, which decreases the risk of occupational exposure. Despite these precautions, workers and people who live near industrial facilities that produce or use EtO may be exposed to EtO through uncontrolled industrial emissions. The general population may also be exposed through tobacco smoke and the use of products that have been sterilized with EtO, such as medical products, cosmetics, and beekeeping equipment.[173]

In 2000, the National Toxicology Program, part of the National Institute of Environmental Health Sciences, upgraded EtO from "reasonability anticipated carcinogen" to a "known human carcinogen."[174] As an analysis conducted by the EPA reaffirmed last year, lymphoma and leukemia are the cancers most frequently reported to be associated with occupational exposure to ethylene oxide. Stomach and breast cancers may also be associated with ethylene oxide exposure.[175]

Because the evidence indicating the carcinogenicity of EtO is well-established, NCI has a limited role in responses to suspected cases of EtO exposure. In these instances, NCI resources may provide data for investigators to determine whether EtO exposure may be contributing to high cancer rates. For example, those investigating such claims may use data collected by the NCI Surveillance, Epidemiology, and End Results (SEER) Program to inform conclusions about how EtO exposure has affected cancer incidence. The SEER Program collects information on cancer in-

[173] https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/ethylene-oxide.
[174] https://www.niehs.nih.gov/news/newsroom/releases/2000/may15/index.cfm.
[175] https://www.tandfonline.com/doi/full/10.1080/15376516.2017.1414343.

cidence, prevalence, and survival from specific geographic areas representing 34 percent of the U.S. population. The SEER research datasets, drawn primarily from State cancer registries, include SEER incidence and population data associated by age, sex, race, year of diagnosis, and geographic areas. SEER also provides analytical tools and methodological expertise in collecting, analyzing, interpreting, and disseminating population-based statistics.[176] Another resource for those investigating instances of EtO exposure is the NCI Cancer Atlas, an exploratory tool that enables users to construct comparative maps, graphs, and charts of cancer statistics and risk factors. The NCI Cancer Atlas can help with the development of new methods of displaying geospatial data for clear communication to the public and for examination of complex multivariate data by researchers.[177] Both the SEER Program and the NCI Atlas can act as resources to inform State and local health departments when assessing cancer incidence and surveillance.

Federal agencies with the authority to research and monitor the effects of hazardous substances on human health are the U.S. Environmental Protection Agency (EPA), the CDC, and the Agency for Toxic Substances and Disease Registry (ATSDR). While the EPA identifies certain chemicals as hazardous air pollutants and regulates facilities with these emissions,[178] the CDC is the lead Federal agency on addressing public health concerns about potential harmful exposures. ATSDR conducts research on the health impacts of specific sites and provides information and recommendations to Federal and State agencies, including CDC and EPA.[179] The National Center for Environmental Health (NCEH), part of CDC, conducts research to investigate the effects of the environment on health by tracking and evaluating environment-related health problems through surveillance systems. NCEH partners with State, local, and tribal health State departments to conduct health surveillance, epidemiologic studies, communication and education, standard setting and guidelines, and technical support.[180]

With technical assistance from CDC, State and local health departments determine whether a particular exposure is responsible for certain cancer cases. NCI assists CDC by supporting epidemiological research on cancer surveillance and studies of cancer incidence, including those programs mentioned above.

NCI will continue to work with other Federal agencies to provide epidemiological data and other research findings to inform their investigation of EtO exposure.

QUESTIONS SUBMITTED TO ANTHONY FAUCI, M.D.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

ANTIMICROBIAL AND ANTIBIOTIC RESISTANCE

Question. Fauci, there was a New York Times article on April 7th describing the rise of drug-resistant germs. The article highlighted that just like bacteria, fungus is now becoming resistant to drugs developed to treat them. Over the past 4 years, the Labor/HHS bill has included specific funds to combat antibiotic resistance, most recently including $550 million in fiscal year 2019 for NIH, 50 percent more than you had in fiscal year 2016. Can you discuss the threat of antibiotic resistant germs and fungus and explain what research your Institute is focusing on in this area?

Answer. The emergence of antimicrobial resistance (AMR) in a range of bacterial and fungal pathogens is a public health threat of great concern. Each year in the United States, there are more than 2 million infections with antibiotic-resistant bacteria and at least 23,000 deaths as a direct result of these infections. Fungal infections also are a serious problem in healthcare settings, and infections with drug-resistant fungi are more difficult to treat. A drug-resistant form of a fungal pathogen, Candida auris (C. auris), recently has emerged in the United States and elsewhere, and has led to severe illness in hospitalized patients. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead Institute of the NIH for basic, translational, and clinical research confronting the critical issue of AMR in bacterial and fungal pathogens.

Advances in AMR research have created opportunities to develop state-of-the-art diagnostics to detect and help limit the spread of AMR, accelerate the development of new antimicrobials, identify ways to use the immune system to eradicate bacterial or fungal pathogens, and manipulate microbial communities to prevent or

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[176] https://seer.cancer.gov/about/factsheets/SEER__Overview.pdf.
[177] https://gis.cancer.gov/gis-nci/gis__nci.html.
[178] https://www.epa.gov/haps.
[179] https://www.atsdr.cdc.gov/about/index.html.
[180] https://www.cdc.gov/nceh/information/about.htm.

treat infections. NIAID has used recent funding increases provided by Congress to expand its comprehensive AMR research portfolio and accelerate research in each of these areas of scientific opportunity.

NIAID supports research to develop rapid point-of-need diagnostics to inform appropriate treatment and identify resistance to commonly used drugs. NIAID research has led to the development of several novel diagnostics capable of distinguishing between numerous infectious agents. These include two Food and Drug Administration (FDA)-cleared diagnostics: one that tests for 24 bacterial and fungal species that cause sepsis, and another that can detect a number of different bacterial and viral species that cause pneumonia along with seven genetic markers of AMR. In addition, the NIAID Antibacterial Resistance Leadership Group, which oversees clinical research on antibiotic resistance, is developing a master protocol to allow for the evaluation of multiple diagnostic tests using samples from a single patient. NIH also is partnering with the Biomedical Advanced Research and Development Authority (BARDA) to support the Antimicrobial Resistance Diagnostic Challenge competition to identify innovative and rapid point-of-need diagnostic tests that inform appropriate antibiotic treatment and facilitate antimicrobial stewardship. Submissions for Step 3 of the Challenge are due in January 2020, and final results of the competition are anticipated in July 2020.

NIAID's investments in AMR research are advancing the development of promising new therapeutic candidates for drug-resistant infections. NIAID-supported researchers have developed a method to synthesize novel forms of a class of antibiotics (tetracyclines) that are not susceptible to existing bacterial resistance mechanisms. One of these compounds, XERAVATM, recently received FDA approval to treat complicated intra-abdominal infections. NIAID funding also has led to the discovery of a new class of antibiotics, malacidins, that are being investigated for further therapeutic development. In addition, NIAID provides in-kind and technical support for CARB–X (Combating Antibiotic Resistant Bacteria-X), a public-private partnership led by BARDA. CARB–X is currently funding the development of 35 innovative projects, including 13 that represent new antibiotic classes.

NIAID also supports the development of antifungal therapies, including those that may be effective against drug-resistant fungi. One fungal pathogen of particular concern is C. auris, which can cause serious infections that can affect the blood, heart, brain, eyes, bones, and other parts of the body. While most C. auris infections are treatable with existing antifungal drugs, the presence of C. auris infections resistant to the main classes of antifungal drugs is extremely concerning. NIAID is facilitating preclinical screening of candidate therapeutics for effectiveness against C. auris and has identified several lead candidates. NIAID also is supporting investigation of a broad-spectrum antifungal with activity against C. auris and other Candida species.

NIAID-supported investigators are exploring approaches that leverage the immune system to combat drug-resistant infections. One novel approach uses antibodies to boost the ability of an infected individual's own immune system to fight infection. NIAID also is advancing the development of candidate vaccines against bacterial and fungal pathogens, including strains that exhibit drug resistance. This includes an experimental vaccine to protect against Staphylococcus and Candida species, including C. auris and Staphylococcus aureus (S. aureus). Vaccines against these bacterial and fungal pathogens could help prevent infections, thus avoiding the use of antibacterial or antifungal drugs and limiting the potential for development of AMR.

NIAID also supports research investigating the use of beneficial bacteria to prevent or treat colonization with pathogenic AMR bacteria. NIAID funds studies on the use of fecal microbiota transplants to replenish beneficial gut microbiota and prevent and treat bacterial infections. This strategy may be particularly effective for difficult-to-eradicate infections such as the bacterial species Clostridium difficile. In addition, NIAID scientists discovered that the use of probiotic digestive supplements containing Bacillus bacteria prevented S. aureus bacteria from growing in the gut and nose of healthy individuals.

NIAID recognizes that a multi-pronged, multi-disciplinary approach is necessary to address the serious threat posed by drug-resistant microbes. NIAID will continue to support the development of improved tools and strategies to identify, prevent, and treat infections with AMR pathogens.

ENDING HIV INITIATIVE

Question. The President's budget proposes to end HIV transmission in the United States in 10 years. Dr. Fauci, can you discuss what is necessary to reach this goal,

how an HIV vaccine could help achieve it, and where you are in the development of a vaccine?

Answer. The fiscal year 2020 President's Budget has proposed a new initiative of the Department of Health and Human Services (HHS) on Ending the HIV Epidemic to address the ongoing public health crisis of HIV in this country. The goals of the initiative are first reducing numbers of new HIV infections in the United States by 75 percent within 5 years, and then by 90 percent within 10 years. The initiative will leverage critical scientific advances in HIV prevention, diagnosis, treatment, and care by coordinating the highly successful programs, resources, and infrastructure of the NIH, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, and the Indian Health Service.

The initiative is coordinated by the HHS Office of the Assistant Secretary of Health. During the initial phase of the initiative, the focus will be on geographic areas and demographic groups in 19 States, Washington, DC, and Puerto Rico, where the majority of new HIV cases are reported, as well as in 7 States with a disproportionate occurrence of HIV in rural areas. The initiative includes four pillars to help reduce HIV infections:

—Diagnose all individuals with HIV as early as possible after infection;

—Treat HIV infection rapidly and effectively to achieve sustained viral suppression;

—Prevent at-risk individuals from acquiring HIV, including through the use of pre-exposure prophylaxis (PrEP); and

—Rapidly detect and respond to emerging local epidemics of HIV infection to further reduce new infections.

Advances in HIV treatment and prevention research suggest that, theoretically, the HIV epidemic in this country could be ended by expanding access to treatment to all persons with HIV and PrEP to all those at high risk. The Administration has developed a practical, achievable plan to focus on the places and populations in the United States that are most affected by HIV. Lessons learned and effective strategies emanating from this initiative would ultimately be applied to profoundly reduce HIV incidence nationwide through Federal, State, and local health departments and nongovernmental organizations. NIH-supported research through the Centers for AIDS Research (CFARs) and AIDS Research Centers will play a critical role in developing best practices for the initiative by collecting and disseminating data on the effectiveness of approaches used to achieve the initiative's four pillars. The fiscal year 2020 President's Budget includes $6 million for NIH CFARs to support the HHS Ending the HIV Epidemic initiative.

The development of a safe and effective HIV vaccine remains a key component to realizing an end to the HIV pandemic. If an HIV vaccine were to become available, it would add another key HIV prevention tool to complement the ongoing efforts on HIV diagnosis, treatment, and pharmaceutical-based prevention through this initiative. NIAID is the lead for HIV vaccine research at the NIH. Currently, NIAID-supported scientists around the world are following two complementary paths to accelerate the development of an HIV vaccine.

The first approach to HIV vaccine development builds upon prior partial success of the RV144 vaccine regimen. In 2009, the findings of a large international clinical trial of the RV144 vaccine regimen showed for the first time that an HIV vaccine approach could confer modest protection against HIV. Today, NIH and our global partners are continuing to build upon the findings from the RV144 trial. Two large HIV vaccine efficacy clinical trials are now ongoing in southern Africa, one to evaluate an experimental vaccine regimen based on the one used in the RV144 trial, and another to assess an experimental "mosaic" vaccine candidate designed to induce immune responses against a wide variety of global HIV strains. Results from these trials are expected in 2022 and 2021, respectively.

NIAID scientists also are pursuing a second, theoretical path that involves studying the body's immune response to HIV infection and finding various ways to generate and enhance that response through vaccination. One theoretical approach involves designing vaccine strategies to generate cellular immune responses capable of protecting against HIV infection. Another promising strategy seeks to identify potential HIV vaccine targets by uncovering the molecular structure of the virus. An additional theoretical approach involves the design of a vaccine that elicits broadly neutralizing antibodies, or antibodies to HIV that can target multiple different HIV strains. Studies are underway to determine whether delivery of such antibodies could provide long-acting protection against HIV infection, similar to the way a traditional vaccine approach would work. Two large clinical trials with sites in the Americas, Europe, and Africa are currently evaluating VRC01, a broadly neutralizing antibody developed by the NIAID Vaccine Research Center. In addition, planning is underway for early phase clinical trials of a three-pronged antibody capable

of binding to three different critical sites on the surface of HIV. NIAID scientists and public-private partners are developing this "tri-specific" antibody with the expectation that it could eventually be used for long-acting HIV prevention and treatment. NIAID scientists also are conducting a Phase 1 clinical trial of a therapeutic HIV vaccine regimen that uses an adjuvanted DNA vaccine "prime" followed by a viral vector "boost" in participants with HIV. The goal of this vaccine strategy is to achieve prolonged undetectable levels of HIV, eliminating the need for lifelong anti-retroviral therapy.

These scientific advances and ongoing investigations provide cautious optimism that the development of a safe and effective HIV vaccine is making headway. It is important to note that even a moderately effective HIV vaccine could substantially slow the HIV pandemic, if optimally implemented with current treatment and prevention modalities. NIAID is committed to the goal of developing a safe and effective HIV vaccine that would complement the HHS Ending the HIV Epidemic initiative and help end the HIV pandemic.

QUESTIONS SUBMITTED TO RICHARD J. HODES, M.D.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

ALZHEIMER'S DISEASE

Question. Dr. Hodes, Dr. Randy Bateman, a researcher at Washington University in St. Louis, has developed a blood test that can detect the build-up of the Alzheimer's protein amyloid years before symptoms appear. This is a significant step toward predicting who will develop dementia. Further, another Washington University researcher, Dr. Gregory Van Stavern, has developed an eye scan that detects changes in the retina that may be able to predict Alzheimer's before dementia begins. These tools could ultimately save millions in healthcare costs because instead of paying thousands of dollars for a PET scan or a spinal tap, you will be able to detect the disease through only a blood test. Can you talk about the progress of this breakthrough as well as other potential ways to better detect Alzheimer's disease?

Part of the issue with the recent drug failures is that may be targeting individuals too late in the disease progression process. Two years ago, you and I visited the Alzheimer's prevention trial in Medellin, Colombia that focuses on a family that is genetically predisposed to early-onset Alzheimer's disease. Can you discuss what research your Institute is supporting to prevent or delay Alzheimer's disease?

Answer. Early detection of pathology consistent with Alzheimer's disease or a related form of dementia (AD/ADRD) opens a "window of opportunity" for us to target the disease before clinical symptoms appear. NIA supports studies exploring a variety of methods to detect AD/ADRD pathology prior to the appearance of symptoms, as well as to identify early, subtle signs of disease while cognitive abilities are still largely intact.

The work of Dr. Bateman, who is affiliated with the NIA-supported Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC) at Washington University, uses subtypes of the amyloid beta protein in the blood to infer the presence of damaging amyloid buildup in the brain. Specifically, they have found that the ratio of two subtypes, amyloid beta 42 and 40, can indicate elevated brain amyloid. Multiple companies have now begun commercial development of diagnostic tests based on the amyloid beta 42/40 ratio.

Other researchers are also working to identify blood-based biomarkers for early detection of AD/ADRD. For example, investigators with NIA's Intramural Research Program recently used advanced machine learning techniques to identify a panel of 26 blood and brain metabolites that were—when present in altered concentrations in blood—consistently associated with brain atrophy, cerebrospinal fluid measures of Alzheimer's pathology, cognitive performance, and disease risk before clinical symptoms appeared. Another team is using changes in autoantibodies—part of the body's immune response—as blood-based biomarkers to detect early AD/ADRD. Still another is testing special "indicator cells" as a biosensor for AD pathology.

Dr. Van Stavern, also affiliated with the Knight ADRC, used a noninvasive eye scanning technique, optical coherence tomography (OCT) angiography, to detect thinning in the retina as well as alterations in retinal blood flow among older people without clinical symptoms of AD/ADRD. These findings correlated with elevated levels of amyloid and tau proteins as detected by PET scan and cerebrospinal fluid examination.

Other ongoing, NIA-supported research using ocular biomarkers to detect early AD/ADRD includes a study correlating amyloid and tau levels in the fluid of the eye

with OCT and cognitive testing for early detection of Alzheimer's disease. Elsewhere, NIA-supported investigators are using an innovative imaging method to detect Alzheimer's pathology, disease progression, and treatment response in people with Alzheimer's and in mouse models of the disease. In this study, individuals drink a solution made with curcumin, a component of the spice turmeric. The curcumin acts as a tracer, "lighting up" amyloid in the eye and enabling its detection with a custom-built high-definition scanning instrument.

In addition, NIA-supported investigators are exploring changes in smell, gait, personality, and even driving behaviors as early warning signs of incipient dementia. Ultimately, we hope to be able to intervene either with or prior to the earliest appearance of symptoms and thereby avoid progression to the later, devastating stages of disease.

Research to prevent or delay AD/ADRD symptoms in at-risk and/or presymptomatic individuals remains a high priority at NIA. The Alzheimer's Prevention Initiative (API) Autosomal Dominant Alzheimer's Disease Trial in Medellin, Colombia is one such study. Recruitment for this trial of the anti-amyloid agent Crenezumab among members of a family at very high genetic risk for developing the disease has been completed, and we anticipate reporting results in 2022. This study is one of several being conducted by the API, the goal of which is to identify pre-symptomatic interventions that will postpone, slow, or prevent the disease's progression.

Another major initiative, the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN–TU), is an international partnership dedicated to designing and managing clinical trials for individuals at high genetic risk of developing AD.

The recently funded DIAN–TU Primary Prevention Trial is a 4-year study of two drugs, Solanezumab and Gantenerumab—antibodies that interact with different forms of amyloid—in 160 asymptomatic individuals at high genetic risk. Investigators will determine whether it is possible to prevent amyloid deposition in this population and if doing so will prevent the cascade of pathology associated with AD and, ultimately, dementia, in people who are otherwise certain to get the disease.

In addition to these highly visible initiatives, NIA also supports studies of physical activity and exercise, diet, and cognitive training to prevent cognitive decline and dementia. Participants in many of these studies are at well-established risk of developing dementia but do not yet show evidence of cognitive decline.

A new, NIA-funded Alzheimer's Clinical Trial Consortium (ACTC) will help investigators harness best practices and latest methods for both treatment and prevention trials. The ACTC includes 35 sites in the United States and will address the complexity, time, and expense of participant recruitment and site activation to find new and effective ways to treat or prevent these devastating disorders.

QUESTIONS SUBMITTED TO NORA VOLKOW, M.D.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

OPIOID RESEARCH AND DATA COLLECTION FROM SAMHSA

Question. Dr. Volkow, our Committee has invested significant resources into opioid treatment, prevention, education, and research. In particular, we now provide States with $1.5 billion in flexible State Opioid Response grants and require States to report to SAMHSA on how they are spending this funding. I believe it is incredibly important that we understand what opioid programs are working and how to replicate those programs across the country. Can you discuss (1) whether NIH researchers have access to this valuable State-by-State data; and (2) what research your Institute is undertaking to better understand what programs work and which do not in opioid prevention and treatment?

Answer. (1) NIH researchers can gain access to data collected in conjunction with SAMHSA grants, such as the State Targeted Opioid Response and State Opioid Response (STR and SOR) grants, through State substance use agencies.

(2) Determining which prevention and treatment approaches are most effective is central in addressing the opioid crisis, and this is precisely the goal of our HEALing Communities Study. Launched in partnership with SAMHSA on April 18, 2019, this multisite implementation research study tests the impact of an integrated set of evidence-based interventions across healthcare, behavioral health, justice, and other community-based settings. The ultimate goal is to generate the evidence needed to determine the most effective strategies for preventing and treating opioid misuse and opioid use disorder (OUD) within highly affected communities. This Study will examine the effectiveness of coordinated systems of care designed to reduce overdose fatalities and events; decrease the incidence of OUD; increase the number of individ-

uals receiving medication to treat OUD, retained in treatment, and receiving recovery support services; and increase the distribution of naloxone.

The HEALing Communities Study includes at least 15 communities in each of four participating States to measure the impact of these targeted strategies. The four institutions leading this research—University of Kentucky, Boston Medical Center, Columbia University, and The Ohio State University—were required to demonstrate their partnership with State governments, and specifically how they plan to leverage SAMHSA funding (such as STR and SOR funding) to provide evidence-based prevention and treatment services. RTI International, based in North Carolina, will serve as the study's coordinating center, and will be responsible for data analysis, health economics research, and widespread dissemination of research findings over the course of the study, under provisions that safeguard the privacy and confidentiality of respondents. The data generated by this Study will inform best practices for other States looking to maximize the impact of their SAMHSA grant funds.

Question. What barriers exist for NIH and SAMSHA to partner on data sharing and how can we help make sure this data is available to the research community?

Answer. NIH has benefitted from a long-standing partnership with SAMHSA that facilitates the translation of sound research into effective practice and policy. SAMHSA and NIH are in regular contact regarding the need for data to be available to researchers. Currently, researchers access data compiled for monitoring SAMHSA grants through State substance use agencies. This is occurring in a number of recently awarded NIH-funded studies. For example, there are currently five studies underway to test approaches for expanding medications for OUD in the context of SAMHSA STR and SOR grants issued under RFA–DA–18–005 (with another three studies underway with support from the Arnold Foundation). In addition, NIH's National Center for Complementary and Integrative Health recently funded five projects examining the impact of behavioral and complementary health interventions within the context of States' plans for using SAMHSA's STR and SOR grant funds.

NIH continues to be committed to working with SAMHSA to find innovative ways to mutually share data and to ensure the data are available to the research community in order to maximize the impact of the research.

SUBCOMMITTEE RECESS

Senator BLUNT. The subcommittee stands in recess.

[Whereupon, at 11:45 a.m., Thursday, April 11, the subcommittee was recessed, to reconvene subject to the call of the Chair.]